CLINICAL VALIDATION TEST OF ARTIFICIAL INTELLIGENCE ASSISTED IN SKIN CANCER SCREENING SYSTEM ON SMARTPHONE APPLICATION

BY

MISS THORFUN TREEWATANAKUL

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE (DERMATOLOGY)
CHULABHORN INTERNATIONAL COLLEGE OF MEDICINE
THAMMASAT UNIVERSITY
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MISS THORFUN TREEWATANAKUL

ENTITLED

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was approved as partial fulfillment of the requirements for
the degree of Master of Science (Dermatology)

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ABSTRACT

Background: Deep learning has been reported to outperform other handcrafted machine learning (ML) algorithms in classification of pigmented skin lesions. To develop reliable, portable, automated diagnosis system with high diagnostic performances is essential for skin cancer screening and diagnosis regardless of specialized dermatologists.

Objectives: To validate the diagnostic performances of artificial intelligence (AI) assisted in skin cancer screening system compared to Board-certified dermatologists versus experienced dermoscopic specialized dermatologists using dermoscopic images in clinical practice.

Methods: Retrospective, descriptive study using 200 randomly selected dermoscopic images of pigmented skin lesions (PSLs); 31 melanomas, 65 nevi, 52 seborrheic keratoses, 6 squamous cell carcinomas, 39 basal cell carcinomas, and 7 other lesions from the medical records in Samitivej Sukhumvit Hospital, Bangkok, Thailand. We examined our AI system' s performance against three board- certified dermatologists versus three experienced dermoscopic specialized dermatologists.

Results: AI system showed higher sensitivity (67.7%) in melanoma diagnosis compared to Board-certified dermatologists (22.6%) and almost the same level as dermoscopic specialized dermatologists (69.9%).

Conclusion: Our artificial intelligence system using deep learning method achieves performance in diagnosis of melanoma with a same level as Board-certified dermatologists. However, AI system still need further trainings to improve its outcomes before applying in clinical settings especially in both squamous cell carcinomas and basal cell carcinomas categories.

Keywords: Artificial intelligence, deep learning, dermoscopy, melanoma, skin cancer, screening system, mobile application

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TABLE OF CONTENTS

	Page
ABSTRACT	(1)
ACKNOWLEDGEMENTS	(3)
LIST OF TABLES	(7)
LIST OF FIGURES	(8)
LIST OF ABBREVIATIONS	(11)
CHAPTER 1 INTRODUCTION	1
1.1 Background and Rationale	1
1.2 Research question	2
1.3 Specific objective	2
1.4 Hypothesis	3
1.5 Keywords	3
1.6 Operation definition	3
1.7 Ethical consideration	3
1.8 Limitation	3
1.9 Expected benefits and application	3
1.10 Obstacles and strategies to solve the problems	4
CHAPTER 2 REVIEW OF LITERATURE	6
2.1 Pigmented skin lesions	6
2.1.1 Benign	6
2.1.2 Skin cancers	12
2.2 Skin cancer diagnosis	15

2.2.1 Visual examination (Naked eyes) 15
2.2.2 Non-invasive imaging tools 16
2.2.2.1 Dermoscopy 19
(1) The Heuristic approach 20
(2) The Analytical approach 25
2.2.3 Histopathological examination 26
2.3 Computer aided diagnosis in skin cancers 27
2.3.1 Artificial intelligence 30
2.3.2 Deep learning 31

CHAPTER 3 RESEARCH METHODOLOGY 38

3.1 Materials 38
3.1.1 Dermoscopic images of pigmented skin lesions 38
3.1.1.1 Test dataset 38
(1) Sample size 38
(2) Inclusion criteria 38
(3) Exclusion criteria 39
3.1.1.2 Trained dataset 39
3.2 Research design 42
3.2.1 Research location 42
3.2.2 Research procedures 43
3.2.3 Outcome measurements 45
3.3 Data analysis 45

CHAPTER 4 RESULTS AND DISCUSSION 48

4.1 Results 48
4.1.1 Diagnostic performances of each type of pigmented skin lesions 48
4.1.1.1 Board-certified dermatologists 48
4.1.1.2 Experienced dermoscopic specialized dermatologists 51

4.1.1.2 Artificial intelligence system (Deep learning) 54
4.1.2 Comparison of skin cancer diagnostic performances among three groups 56
4.1.3 Comparison of pigmented skin lesions diagnostic performances among three groups 61
4.2 Discussion 66

CHAPTER 5 CONCLUSIONS AND RECOMMENDATIONS 71

5.1 Conclusions 71
5.2 Recommendations 71

REFERENCES 72

APPENDICES 80

APPENDIX A CASE RECORD FORM 81
APPENDIX B TEST DATASET FOR DERMATOLOGISTS 82
APPENDIX C ANSWER SHEET 83
APPENDIX D SMARTPHONE APPLICATION OF AI ASSISTED IN SKIN CANCER SCREENING SYSTEM 84

BIOGRAPHY 85

LIST OF TABLES

Tables		Page
1.1	Administration and time schedule	6
2.2.2	In vivo imaging techniques for the diagnosis of skin cancer	17
2.2.2.1.1a	ABCD rule of dermoscopy (Modified 1994)	23
2.2.2.1.1b	The 7-point checklist	24
2.2.2.1.1c	Menzies' method for the diagnosis of melanoma	25
2.3.2	Area under ROC curve of different methods on diagnosis of melanoma, nevus, and seborrheic keratosis	35
3.1.1.2	Sources of trained dataset	40
4.1.1.1	Mean diagnostic performances of Board-certified dermatologists in diagnosis of different pigmented skin lesions	48
4.1.1.2	Mean diagnostic performances of experienced dermoscopic specialized dermatologists in diagnosis of different pigmented skin lesions	51
4.1.1a	Interclass correlation coefficient (ICC)	52
4.1.1.3	Diagnostic performances of artificial intelligence system in diagnosis of different pigmented skin lesions	54
4.2	Sources of trained dataset	68

LIST OF FIGURES

Figures		Page
2.1.1.1	Acquired melanocytic nevi	7
2.1.1.2	Seborrheic keratosis	7
2.1.1.3	Spitz nevus	8
2.1.1.4	Reed nevus	8
2.1.1.5	Blue nevus	9
2.1.1.6	Nevus spilus	9
2.1.1.7	Congenital melanocytic nevi	10
2.1.1.8	Atypical melanocytic nevus	11
2.1.1.9	Solar lentigines	11
2.1.1.11	Dermatofibroma	12
2.1.2.1	The four most common types of melanoma	13
2.1.2.2	Basal cell carcinoma	14
2.1.2.3	Squamous cell carcinoma	15
2.2.2.1.1a	The Pattern Analysis (Two steps algorithm)	20
2.2.2.1.1b,c	Stepwise evaluation of dermoscopic features of Pattern Analysis (Two steps algorithm)	21
2.2.2.1.1d	Criteria for melanocytic lesions	22
2.2.2.1.1e	Benign and malignant patterns of volar aspects	22
2.2.2.1.2	The analytic approach (Chaos & Clues method)	26
2.3	CAD steps to help in diagnosis of pigmented skin lesions	27
2.3.2a	Flowchart of algorithms used to classify melanoma, seborrheic kerratosis, and nevus.	28
2.3.2b	Dermoscopic images of malignant melanoma from ISIC-ISBI Challenge 2017	28
2.3.2c	Example network architectures for CNNs. Right: a residual network with 34 parameter layers	29
2.3.2d	A deep DenseNet with three dense blocks.	29
2.3.2e	Diagram of 3-Binary DenseNet121 classifier and 3-Binary ResNet50 Classifier	35

2.3.2f	Average ROC ± SD of four algorithms and the average AUC ± SD for melanoma(MM) classification	36
2.3.2g	Flowchart of scientific development design in this study	37
3.1.1a, b	Examples of dermoscopic images of melanoma	41
3.1.1c	FotoFinder Hub® system (FotoFinder Systems GmbH, Deutschland)	42
3.2.2	Flow chart of study procedures	43
3.2.2.3a,b	Examples of validation test for dermatologists	44
3.3.1	Diagnostic parameters	46
4.1.2.1a	Diagnostic performances in diagnosis of different types of skin cancers; three Board-certified dermatologists and mean values	50
4.1.2.2a	Diagnostic performances in diagnosis of different types of skin cancers; three experienced dermoscopic specialized dermatologists and mean values	53
4.1.1.3	Confusion matrix of AI system performance	55
4.1.2.1	Sensitivities in diagnosis of different types of skin cancers compared among three groups	56
4.1.2.2	Specificities in diagnosis of different types of skin cancers compared among three groups	57
4.1.2.3	Accuracies in diagnosis of different types of skin cancers compared among three groups	58
4.1.2.4	Positive predictive values(PPV) in diagnosis of different types of skin cancers compared among three groups	59
4.1.2.5	Negative predictive values(NPV) in diagnosis of different types of skin cancers compared among three groups	60
4.1.3.1	Sensitivities in diagnosis of different types of benign pigmented skin lesions compared among three groups	61
4.1.3.2	Specificities in diagnosis of different types of benign pigmented skin lesions compared among three groups	62
4.1.3.3	Accuracies in diagnosis of different types of benign pigmented skin lesions compared among three groups	63

4.1.3.4	Positive predictive values(PPV) in diagnosis of different types of benign pigmented skin lesions compared among three groups	64
4.1.3.5	Negative predictive values(NPV) in diagnosis of different types of benign pigmented skin lesions compared among three groups	65
4.2.1a,b,c	Clinical dermoscopic images in test dataset	66
4.2.2a	Confusion matrix of AI system performance: melanoma classification	67
4.2.2b	Confusion matrix of AI system performance: BCC classification	69
4.2.2c	Confusion matrix of AI system performance: SCC classification	70

LIST OF ABBREVIATIONS

Symbols/Abbreviations	Terms
α	Alpha
AI	Artificial intelligence
β	Beta
BCC	Basal cell carcinoma
BMC-IRB	Institutional Review Board of Bangkok Hospital Medical Center
CAD	Computer aided detection
CADx	Computer aided diagnosis
cm	Centimeter
CNNs	Convolutional neural networks
CSLM	Confocal scanning laser microscopy
CT scan	Computerized Tomography scan
DARPA	The Defense Advanced Research Projects Agency
DenseNets	Densely Convolutional Networks
DL	Deep learning
DNA	Deoxyribonucleic acid
e.g.	For example
ELM	Epiluminescence microscopy
Fig	Figure
FN	False negative
FP	False positive
GANs	Generative Adversarial Networks
GPU	Graphics processing unit
HFU	High frequency ultrasound
ICC	Interclass Correlation Coefficient
ISIC	International Skin Image Collaboration

ISIC- ISBI	International Symposium on Biomedical Imaging Hosted by the International Skin Image Collaboration
KNN	K-Nearest Neighbors
ML	Machine learning
mm	millimeter
MM	Malignant melanoma
MRI	Magnetic resonance imaging
n	Sample size
NPV	Negative predictive values
NV	Nevus
OCT	Optical coherence tomography
Others	Other diagnosis
p	Proportion
p0	Reference value
PET	Positron emission tomography
PPV	Positive predictive values
PSLs	Pigmented skin lesions
ResNets	Deep Residual Neural Networks
RMC-IRB	Institutional Review Board of Bangkok Hospital Medical Center
ROC curve	Receiver Operating Characteristic curve
SD	Standard deviation
SebK	Seborrheic keratosis
SK	Seborrheic keratosis
SPSS	Statistical Package for Social Sciences
3D	Three dimensions
TBSE	Total body skin examination
TDS	Total dermoscopy score
TLM	Transillumination
TN	True negative

TP	True positive
U.S.	United States of America
WGAN-GP	Wasserstein-Generative Adversarial Network with gradient penalty
XLM	Cross-polarization epiluminescence

CHAPTER 1
INTRODUCTION

1.1 Background and Rationale

Pigmented skin lesions (PSLs) are included both benign and malignancy. Melanoma, a malignant form of PSLs, is the most aggressive and life-threatening skin cancer. The statistic of global cancers shows that the incidence rates and mortality rates of malignant melanoma are increased every year. Although early stages are highly survivable, melanoma can rapidly spread and become fatal. 5-year survival rate of melanoma drops from 97% in the earliest stage to 10% in the latest stage. Therefore, early detection of melanoma is critical to reduce morbidity and mortality rates of patients. However, overdiagnosis may lead to unnecessary biopsies, which possibly results in adverse effects.

Diagnosing melanoma begins with visual examination. Only 60% of clinical accuracy in diagnosis with naked eyes has been reported for dermatologists in the specialized centers. Dermoscopy, which is a microscopic imaging tool for pigmented skin lesions diagnosis, significantly improved the accuracy compared with inspection by naked eyes but only in specialized well-trained physicians. Moreover, diagnosis of early stage of melanoma is still challenging even for experienced dermatologists.

To overcome these limitations, computer aided diagnosis system has been introduced. Deep learning, a subtype of machine learning, has been used in several fields due to outperformance over other handcrafted machine learning algorithms particularly in visual task such as face recognition, object classification, playing strategic board game like Go, and medical screening which has been shown to exceed human performances.

Thai researchers team has trained AI with four high potential algorithms in classification of melanomas, nevi, and seborrheic keratoses by using dermoscopic images from International Skin Imaging Collaboration (ISIC) 2017 dataset. The result showed that Densely Convolutional Network (DenseNet-121), one of four deep

learning algorithm network, performed the best in sensitivity, specificity, and accuracy up to 80-90%. Moreover, with the help of artificial training images generated from WGAN- GP can solve the problem of scarcity of training data and improve classification outcome of melanoma.

1.2 Research question

Although the computer aided diagnosis of melanoma had high sensitivity, specificity, and accuracy under experimental conditions, the use of this method in real clinical settings is still unknown.

In this research, we aimed to validate the diagnostic performances of the first artificial intelligence assisted skin cancer screening system in Thailand and compare the diagnostic ability to Board- certified dermatologists and experienced dermoscopic specialized dermatologists using clinical dermoscopic images.

1.3 Specific objective

The primary objective is to validate the diagnostic performances of the artificial intelligence (deep learning) in skin cancers diagnosis including *sensitivity, specificity, accuracy, positive predictive values, and negative predictive values* using clinical dermoscopic images.

The secondary objective is to compare the diagnostic performances of the artificial intelligence with dermoscopic specialized dermatologists vs Board-certified dermatologists in skin cancers diagnosis using dermoscopic images.

1.4 Hypothesis

Artificial intelligence (Deep learning) might achieve performances in diagnosis of skin cancers with a same level as Board-certified dermatologist or dermoscopic specialized dermatologist.

1.5 Keywords

Artificial intelligence
Deep learning
Dermoscopy
Melanoma
Skin cancer screening system
Mobile application

1.6 Operation definition

Clinical dermoscopic images of pigmented skin lesions

1.7 Ethical consideration

The study protocol was granted by Institutional Review Board of Bangkok Hospital Medical Center (BMC-IRB).

1.8 Limitation

Lack of clinical dermoscopic images of skin cancers especially squamous cell carcinomas and basal cell carcinomas used to train artificial intelligence. In addition, colors of images from multi-sources images were different which could lead AI in low diagnostic performances.

1.9 Expected benefits and application

Early detection of melanoma is critical. Advances in computer aided classification of pigmented skin lesions could potentially assist dermatologists or medical practitioners in improving diagnostic accuracy especially in early stage melanoma. Moreover, getting to a dermatologist is rarely easy. To make the algorithm system compatible with mobile application can greatly extend the accessibility of

dermatologists outside of the hospitals and even in the remote areas which lack of specialists. This artificial intelligence technology will allow patients to self-follow up in suspicious pigmented skin lesions and early detect skin cancers from anywhere. Therefore, it provides low-cost access and high reliability to vital diagnostic care. However, rigorous prospective validation of this artificial intelligence assisted skin cancer screening system is necessary before it can be used in clinical practice. So that, this research is designed to test this system as well as compare its performance with standard process.

1.10 Obstacles and strategies to solve the problems

The lack of dermoscopic images of skin cancers especially squamous cell carcinomas and basal cell carcinomas caused low diagnostic performances for AI. The problem was solved by combining clinical dermoscopic images from medical records into the trained dataset for AI. Also, dermoscopic images from reliable textbook were included in the trained dataset.

For adjusting the color of images, the researchers applied color constancy using the Shades of Grey method to improve the outcome.

Table 1.1 Administration and time schedule

	2017	2018						
	DEC	JAN	FEB	MAR	APR	MAY	JUN	JULY
Research proposal								
Research ethics								
Experiment								
Data analysis & conclusion								
Proceeding								
Publishing								

CHAPTER 2
REVIEW OF LITERATURE

2.1 Pigmented skin lesions

Pigmented skin lesions (PSLs) which refer to lesions that are brown, black, blue, grey or red in color, are often melanocytic. (1) They can be classed as benign or malignant. Most pigmented skin lesions are reported as benign nevi, however a small number will be malignancy. (2) They are very similar in morphologies, colors, and textures. To distinguish between malignant and benign moles is challenging task for dermatologists. (3, 4) The following section summarizes the common pigmented skin lesions.

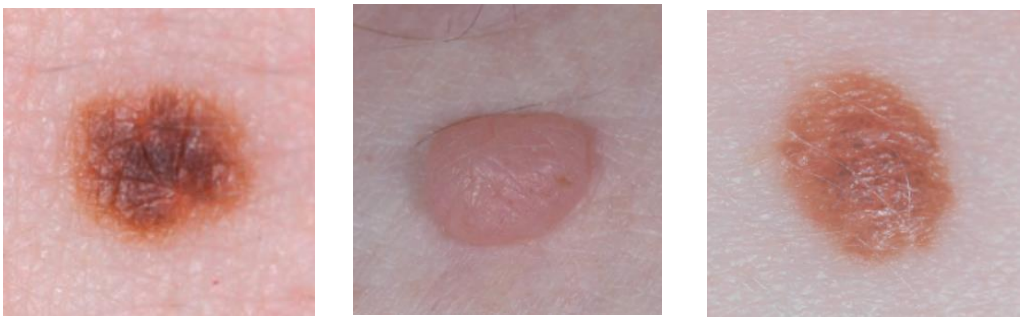
2.1.1 Benign

Benign pigmented skin lesions (PSLs) are harmless, although they are closely related to malignant melanomas. The common benign PSLs are such as acquired melanocytic nevi, seborrheic keratoses, blue nevi, atypical or dysplastic nevi, congenital nevi, pigmented Spitz nevi etc.

2.1.1.1 Acquired melanocytic nevi

Acquired melanocytic nevi, commonly called benign moles, are usually small, pigmented macules, papules, or nodules with sharply demarcated border. They are classified into three groups as listed below. (5)

- **Junctional nevus:** usually small, brown to black macule (*Figure 2.1.1.1a)*
- **Intradermal nevus:** a dome-shaped skin-colored or light to dark brown papule or nodule (*Figure 2.1.1.1b)*
- **Compound nevus:** can be light to dark brown papule or nodule (*Figure2.1.1.1c)*



a) b) c)

Figure 2.1.1.1 Acquired melanocytic nevi. (5)

a) junctional nevus b) intradermal nevus c) compound nevus

2.1.1.2 Seborrheic keratosis

Seborrheic keratosis is a benign epithelial skin neoplasm. It can appear on any site of body especially on face and trunk, but not palms and soles. It usually begins as flat, well-circumscribed, black or brown patches. Then, it may become polypoidal with verrucous and dull surface. "Stuck-on" appearance is the key feature. Its color varies from yellowish to brownish-black. (5, 6)

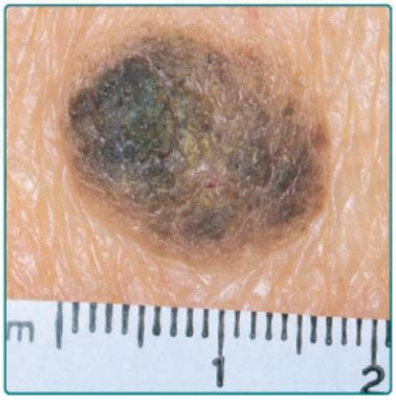


Figure 2.1.1.2 Seborrheic keratosis showing stuck-on appearance. (7)

2.1.1.3 Spitz nevi

It is characterized by a small (<1 cm), dome-shaped, tan or pink nodule with often a history of recent rapid growth. It is very difficult to distinguish from melanoma.

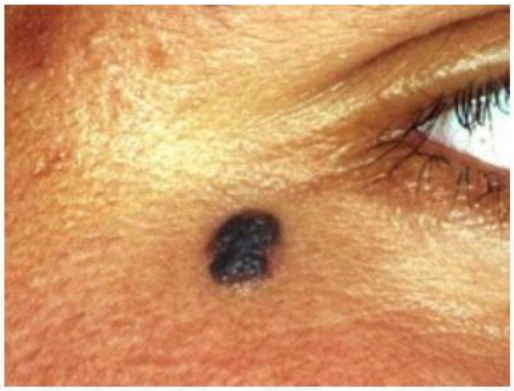


Figure 2.1.1.3 Spitz nevus (8)
Available from https://www.dermnetnz.org/topics/spitz-naevus/

2.1.1.4 Reed nevi

It is characterized as dark brown to black papule or plaque, usually smaller than Spitz nevus. It is often seen in young women around thirty. Lower extremities are common sites.

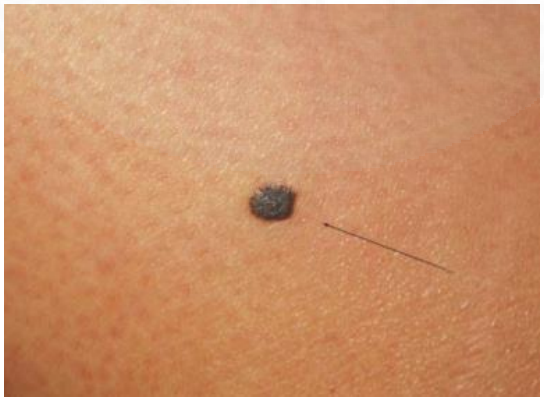


Figure 2.1.1.4 Reed nevus. (9)

2.1.1.5 Blue nevi

The clinical presentation of blue nevi is acquired, firm blue to gray to black, sharply demarcated papule or nodule. About 50% are seen on the dorsal aspect of the hands and feet. Although it is benign, some types of blue nevi may have an elevated risk for development of melanoma.

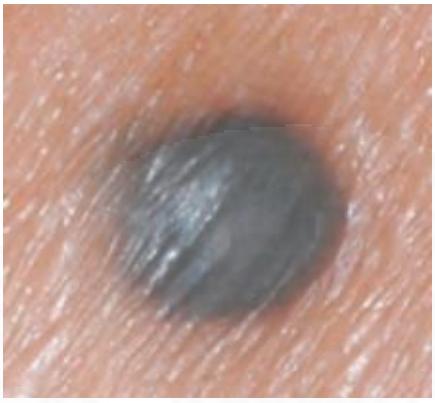


Figure 2.1.1.5 Blue nevus. A well-circumscribed, blue, dome-shaped papule. (5)

2.1.1.6 Nevus spilus

It consists of a light brown macule which vary in size and multiple dark brown small macules (2-3 mm) or papules scattered throughout the pigmented background.

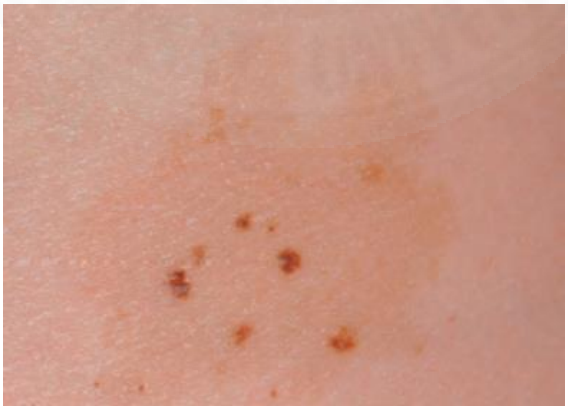


Figure 2.1.1.6 Nevus spilus. Multiple brown macules and papules superimposed upon a tan patch. (5)

2.1.1.7 Congenital melanocytic nevi

It is an abnormality of normal melanocytic development that results in the abnormal accumulation of melanocytic cells along migration pathways. It presents at birth. The lesion is varied in size, usually begins as slightly raised tend with age to become more elevated. Large lesions can more potentially transform to malignant melanoma.

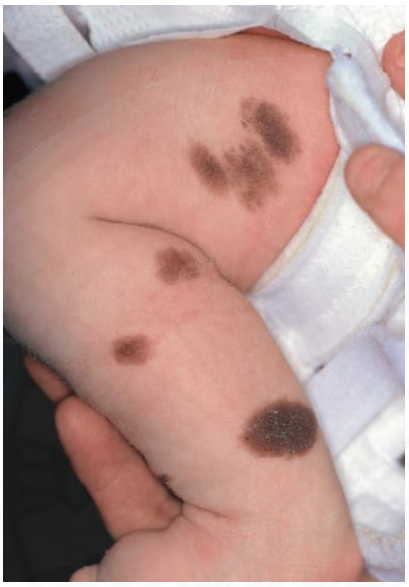


Figure 2.1.1.7 Congenital melanocytic nevi. Multiple medium-sized nevi. (5)

2.1.1.8 Atypical or dysplastic nevi

It is usually larger than 5 mm with irregular borders, often variably pigmented with occasional pink inflammatory appearance, common on trunk and limbs. If a single lesion is present and unchanging for years, it is unlikely to be melanoma.

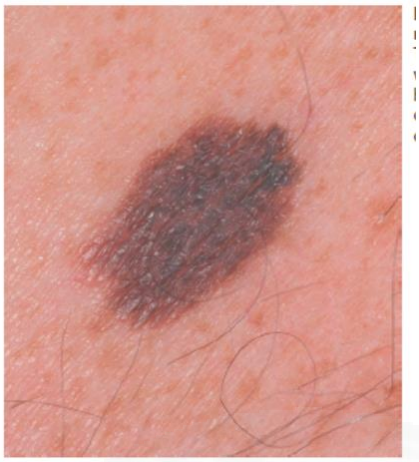


Figure 2.1.1.8 Atypical melanocytic nevus. There is asymmetry as well as several shades of brown, simulating the clinical features seen in cutaneous melanoma. (5)

2.1.1.9 Solar lentigines

They usually present with numerous small (<0.5 mm) brown macules. Sun-exposed areas such as face, arms, and hands are common sites.

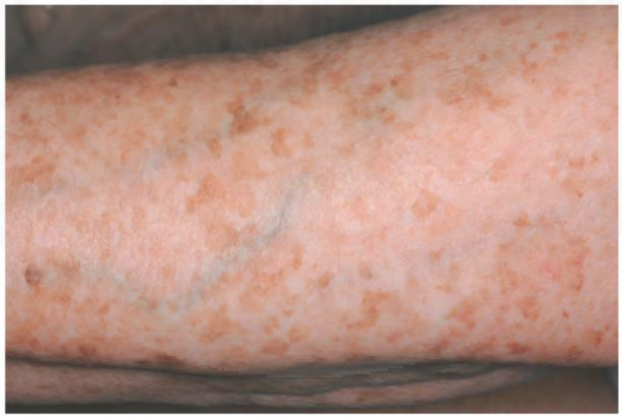


Figure 2.1.1.9 Solar lentigines. (5)

2.1.1.10 Café-au-lait macules

They may be described as homogenous light to dark brown macules with well-defined margins, usually 2-5 cm in diameter, but may vary in size. They can be located anywhere on the body except mucous membranes. These skin lesions are found in both normal population and McCune-Albright syndrome patients.

2.1.1.11 Dermatofibromas

Dermatofibroma is characterized as a button-like dermal nodule commonly seen on the extremities. “Dimple” sign is the key clinical finding. It can be pigmented or non-pigmented.

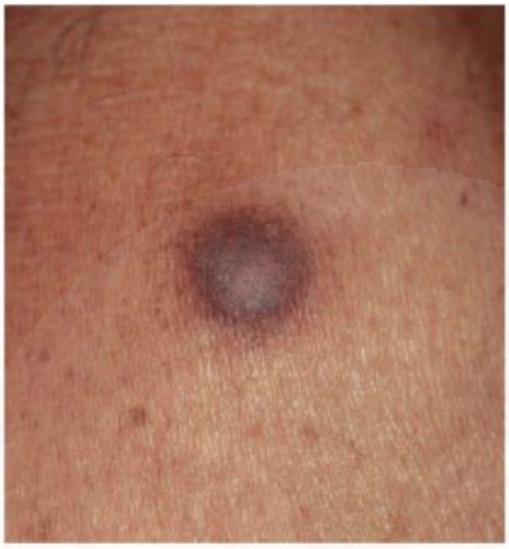


Figure 2.1.1.11 Dermatofibroma. Hyperpigmented firm papule on the lower extremity. (5)

2.1.2 Malignancy

Skin cancers are abnormal growth of skin cells which most often develops on chronically sun exposed skin. There are three main types of skin cancers including malignant melanoma, basal cell carcinoma, and squamous cell carcinoma. Melanomas are often pigmented unlike others.

2.1.2.1 Melanoma

Melanoma is the most aggressive skin cancer. It can develop anywhere on the body and occur either on normal-appearing skin or existing mole. (10) Typical features are asymmetry of the lesion, irregular borders, vary in color, diameter greater than 5 mm, growth of nodules and regression of lesions. Although melanomas are usually pigmented, they can also be amelanotic. There are four major subtypes of melanoma which can be classified according to clinical presentation and histological features. (11)

Superficial spreading melanoma is primarily macule that can slowly develop into a nodule or plaque, often with multiple colors and areas of regression.

Nodular melanoma is often presented as brown to black nodules with eroded or bleeding ulcer.

Lentigo maligna melanoma usually arises slowly from melanoma in situ on the sun-damaged skin.

Acral lentiginous melanoma is typically located on periphery. It is primarily an irregular, poorly defined border pigmentation, later becomes nodule in an invasive growth phase.

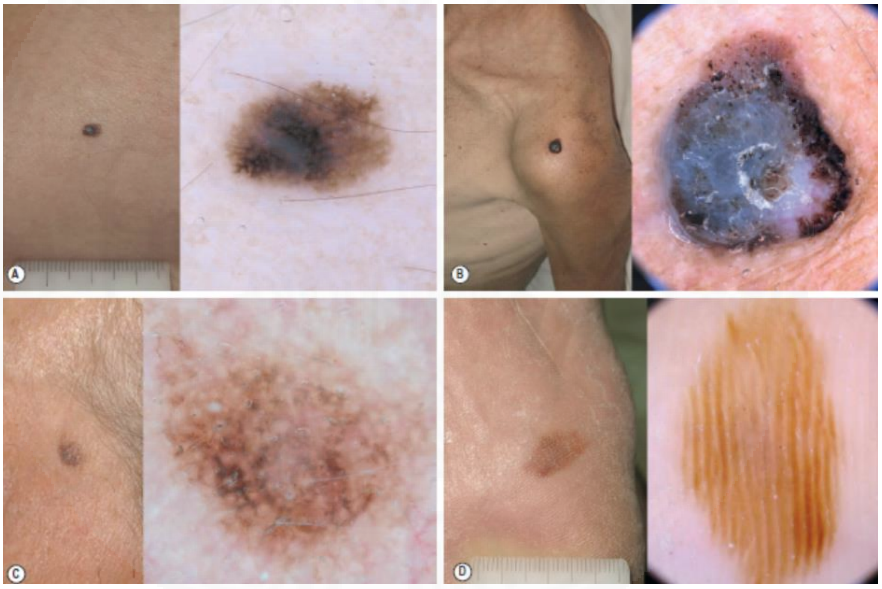


Figure 2.1.2.1 The four most common types of melanoma: clinical and dermoscopic images (5)

a) Small superficial melanoma

b) Nodular type melanoma

c) Small facial melanoma *in situ* (lentigo maligna)

d) Acral melanoma

2.1.2.2 Pigmented basal cell carcinoma

Basal cell carcinoma (BCC) is a tumor that arises within sun-damaged skin. The major risk factor is UV radiation. There are four main clinicopathologic types including nodular, superficial, morpheaform, and fibroepithelial BCC.(5) Although most BCCs are amelanotic, pigmented BCCs can be observed more commonly in those with dark skin types. Classic presentations are pearly rolled border and central hemorrhagic crust or telangiectasia.

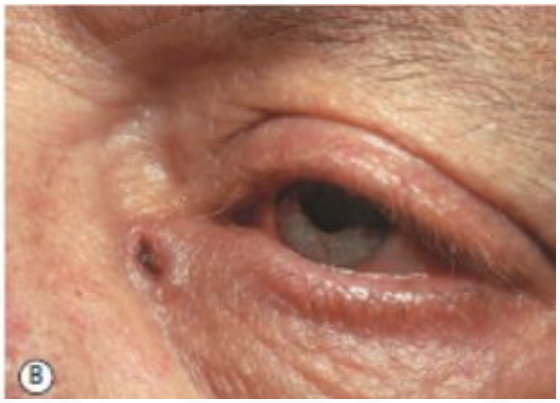


Figure 2.1.2.2 Basal cell carcinoma, nodular subtype (5)

2.1.2.3 Pigmented squamous cell carcinoma

Squamous cell carcinoma (SCC) is a common type of skin cancers. It can appear on any part of the body including lips and genitals. The color usually varies from erythematous to skin-colored, rarely pigmented variants. SCCs are often papulonodular, but can be plaque-like, papillomatous or exophytic. It can be classified into three groups depending on histopathology of lesions.

Actinic keratosis is considered as precancerous or premalignant tumor because atypical keratinocytes are confined within epidermis.

Squamous cell carcinoma in situ which is commonly known as Bowen's disease, is often not aggressive. The most common presentation are erythematous scaly patches or plaques.

Invasive squamous cell carcinoma is the aggressive form of SCC.

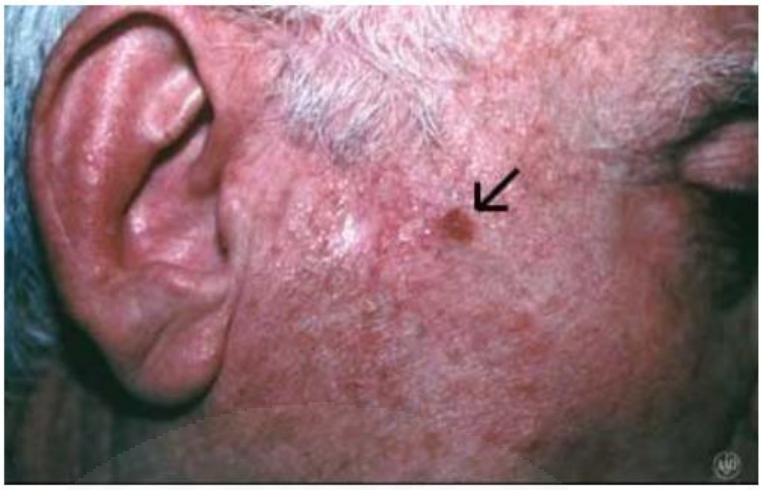


Figure 2.1.2.3 Squamous cell carcinoma on patient's face with sun damaged skin. (7) Available from https://www.aad.org/public/diseases/skin-cancer/squamous-cell-carcinoma

2.2 Skin cancer diagnosis

Malignant melanoma is a lethal form of skin cancers resulting from DNA mutation of melanocytes. (12) The global cancer statistics show that the number of new patients and mortality rates of melanoma are steadily increased every year. (13) This current year, the American Cancer Society estimates that 87,000 new cases and 9,000 deaths will occur in U.S. due to the disease. (14) In the advanced stages of melanoma are incurable and the treatments are mainly palliative, including surgery, immunotherapy, chemotherapy, targeted therapy, and/or radiation therapy. (11, 15-17) Therefore, screening system in early melanoma is thought to improve the prognosis and reduce morbidity and mortality rates of patients.

2.2.1 Visual examination (Naked eyes)

Most malignant melanomas arise on the skin surface and primarily diagnosed by visual examination. The key principle for skin cancer screening techniques is total body skin examination (TBSE). (3)

The clinical diagnosis of dermatologists is based on three analysis steps of pigmented skin lesion. First step is excluding non-melanocytic lesions and searching for suspicious melanocytic lesions. There are many methods used for

identifying suspicious melanocytic lesions such as ABCDE criteria (18) and the Glasgow 7-point checklist (19). The ABCDE approach has been widely used in clinical practice. The rule which “A” stands for asymmetry, “B” stands for border irregularity, “C” stands for color ununiform, “D” stands for diameter greater than six mm, and “E” stands for elevation and/or enlargement of a lesion. (20) Moreover, EFG is being added to the ABCD rule for nodular lesions, including “F” which stands for firm, and “G” stands for growing for one month. (2) Second step is comparative analysis, which is looking for the “ugly duckling sign” or the moles that are not alike the others in the same patient. Last step is to search for rapid growth or recent change of lesions like in “E” and “G” in ABCD rule with additional EGF.

However, unaided visual inspection of pigmented skin lesions is suboptimal. (21, 22) Only 60% of clinical accuracy in diagnosis with naked eyes has been reported even for expert dermatologists in the specialized centers. (23) Another study showed that sensitivity in diagnosis of clinical melanoma of experienced dermatologists is approximately 70%. (24)

2.2.2 Non-invasive imaging tools

Although the best way and the most reliable method to differentiate between benign and malignant lesions are histopathological examination from skin biopsy, there is limitation in scar formation. Therefore, it is greatly important to develop tools for diagnosis skin cancers which have more accuracy than using only naked eyes and also avoid unnecessary excision of benign moles.

Numerous imaging modalities in vivo diagnosis of melanoma have been developed including total cutaneous photography, dermoscopy, confocal scanning laser microscopy (CSLM), high frequency ultrasound(HFU), magnetic resonance imaging (MRI), optical coherence tomography (OCT), positron emission tomography (PET) and multispectral imaging. (3, 25, 26) These non-invasive in vivo imaging tools are important in screening process and tend to improve early detection. Each technique has different pros and cons shown in *Table 2.2.2*

Table 2.2.2 In vivo imaging techniques for the diagnosis of skin cancer (25)

Methods	Advantages	Limitations
Photography	- Affordable and easy data management. - Monitoring patients with many dysplastic nevi. - Useful in the follow-up management and easy comparison for detecting changes that may be suggestive of malignancy.	- Limited morphologic information.
Dermoscopy ELM (oil/slide mode and polarizing mode)	- Facilitating 20–70% magnification of the skin. - Dermoscopic features of skin lesions are correlated to histopathologic characteristics. - Identifying foci of melanoma to help pathologist in decision of where to section specimen. - Liquid immersion provides increased illumination and resolution and sharper and less distorted colors. - Polarizing mode can avoid nosocomial infections.	- Qualitative and potentially subjective. - Low magnification in routinely used instruments.
Multispectral imaging -Melafind -Solar scan	- Spectral imaging is quantitative and more objective. - Less interphysician variability.	- Processes in tumor invasion depth cannot be evaluated accurately.

-Spectrophoto metric intracutaneous analysis	- SIA scope can detect very small skin lesions. - Skin chromophores can be analyzed	- Price of instrument is expensive to use in routine clinical application. - Formal training and experience is required.
Laser- based enhanced diagnosis -Confocal scanning laser microscopy -Reflectance confocal microscopy -Spectrally encoded confocal microscopy	- Can provide information of skin lesions at variable depths and examination at a quasi-histological resolution without biopsy. - High resolution allows imaging of deeper layers of tissue structures. - No tissue damage because of low-power laser.	-Processes in tumor invasion depth cannot be evaluated accurately. -Training and experience is required.
Optical coherence tomography	- Depth of invasion can be better measured with OCT. - Noninvasive assessment and monitor of inflammatory skin diseases.	-Limited resolution does not allow a distinguish between benign versus malignant lesions. -Limited to thin tumors because of the strong scattering of epidermal tissue.

Ultrasound imaging	- Can provide dynamic information such as perfusion phase of lymph nodes and blood vessels that can be facilitated in staging of the skin cancers.	-Accuracy of results depend heavily on the skill of examiner and anatomic site of lesion.
Magnetic resonance imaging	- Obtaining information on thickness and volume of melanoma, also the depth of tumor and underlying tissue involvement.	- Expensive to use in routine clinical application

2.2.2.1 Dermoscopy

Dermoscopy has become an essential tool for dermatologists to distinguish between benign and malignant pigmented lesions. It links clinical and pathologic characteristics by improving the visualization of morphological details which cannot be seen with naked eyes examination. (25) So far, this method is the fastest way to detect skin cancers and most widely used tool in dermatologic clinics. There are different techniques such as solar scan, epiluminescence microscopy (ELM), cross-polarization epiluminescence (XLM), and side transillumination (TLM) which can potentially provide better morphological details for better visualization.

Several publications have been proven the benefit outcomes using dermoscopy in screening system for skin cancers. This microscopic examination significantly improves the clinical diagnosis of pigmented skin lesions (27-29) and enables better diagnosis as compared to unaided eyes. (30, 31) A meta-analysis of several studies showed that dermoscopic experienced practitioners had high performances in melanoma diagnosis of sensitivity 89% and specificity 79%. (32) Moreover, A multicenter study showed that the use of dermoscopy increased sensitivity in melanoma diagnosis and decreased the number of unnecessary biopsied benign

lesions. (4, 26) In European consensus-based interdisciplinary guideline 2016 recommended to use digital dermoscopy in screening and following up high risk patients. (11) Nowadays, there are two major approaches for dermoscopic images; the Heuristic approach or Pattern analysis and the Analytical approach or Chaos and Clues. (33)

(1) The Heuristic approach is also called "The Pattern Analysis." It provides a two steps algorithm to diagnose pigmented skin lesions shown in *Figure 2.2.2.1.1a*

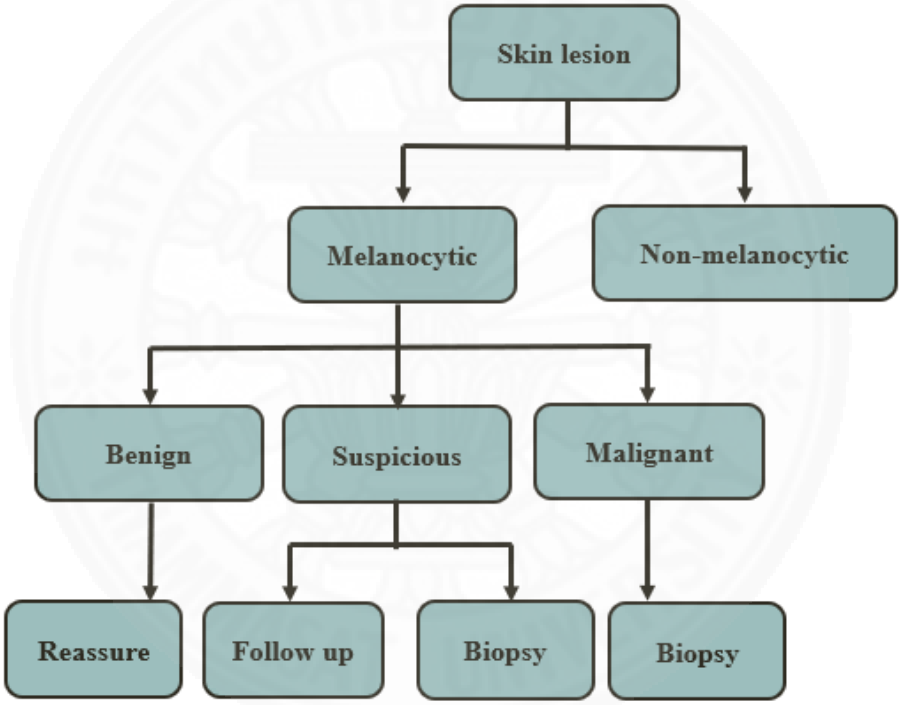


Figure 2.2.2.1.1a The Pattern Analysis (Two steps algorithm)

First of all, you need to classify pigmented skin lesions into melanocytic and non-melanocytic categories by using stepwise evaluation of dermoscopic features shown in *Figure 2.2.2.1.1b, c*

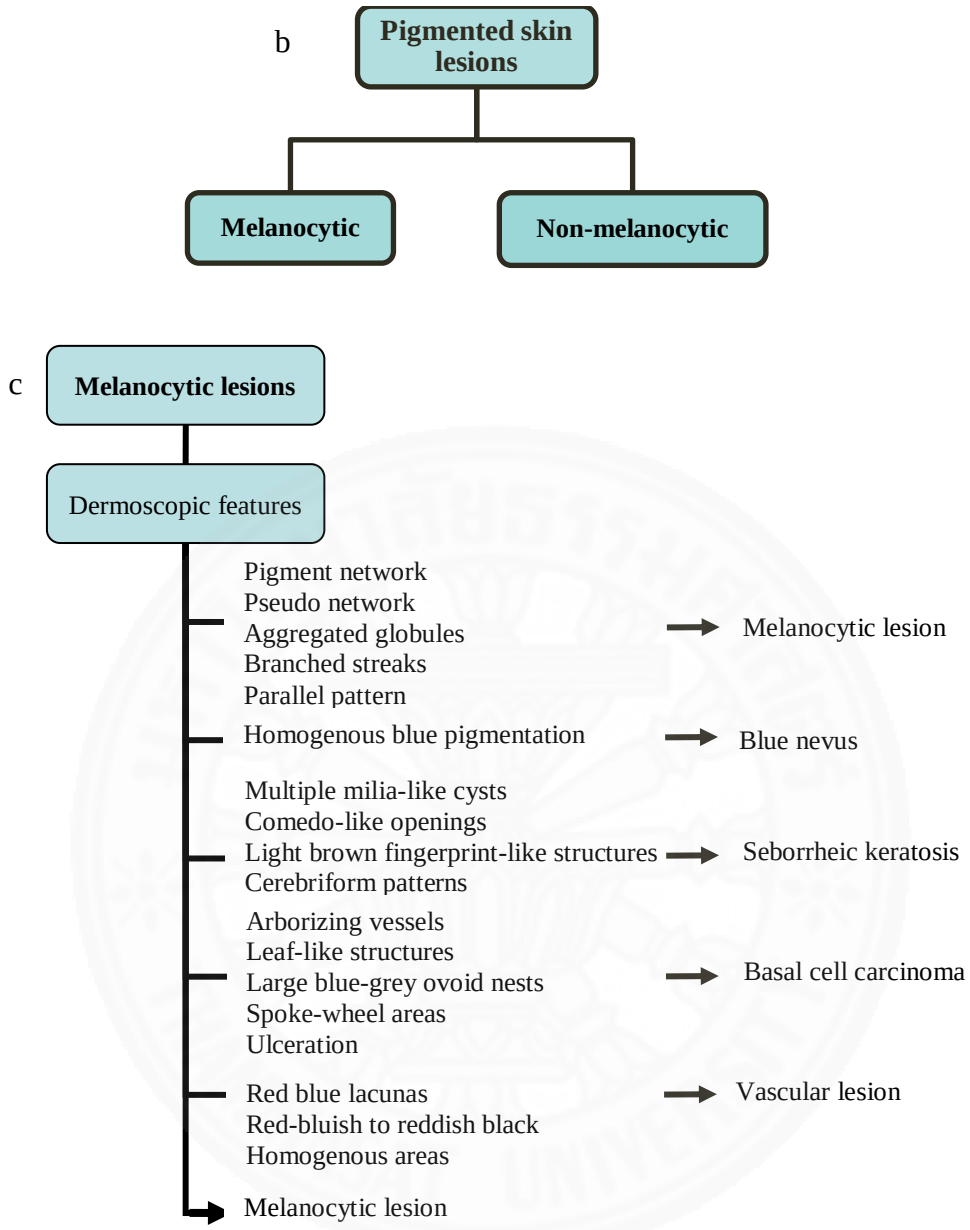


Figure 2.2.2.1.1b, c Stepwise evaluation of dermoscopic features of the Pattern Analysis (Two steps algorithm) (34)

The melanocytic lesion is considered following criteria including pigment network, branched streaks, streaks, negative network, aggregated globules, homogenous blue pigmentation, pseudonetwork (face), or parallel pattern (palms, soles, and mucosa). (see *Figure 2.2.2.1.1d* and *2.2.2.1.1e*)

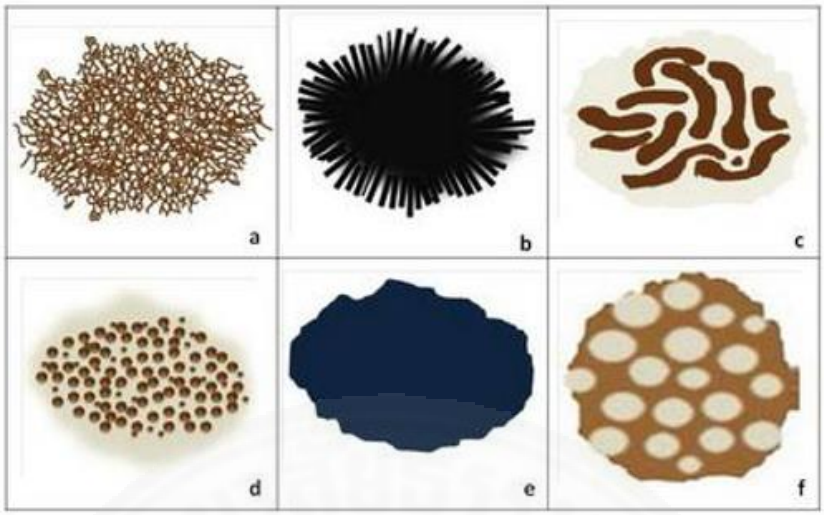


Figure 2.2.2.1.1d Criteria for melanocytic lesions (33)

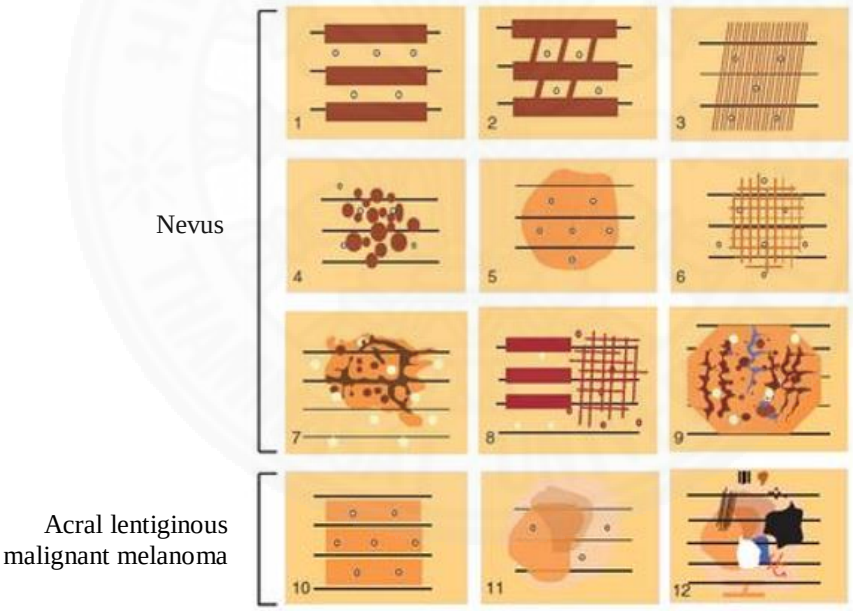


Figure 2.2.2.1.1e Benign and malignant dermoscopic patterns of volar areas (33)

Second, you need to consider whether the melanocytic lesion is benign, suspected or malignant. In this step, many different algorithms can be proposed such as the 7-point checklist (35), Three-point checklist (36), Pattern analysis (37), ABCD rule(38), Menzies' method etc. (33) These followings are the summaries of common approaches.

ABCD rule of dermoscopy being introduced by Stolz and coworkers has been proven to be a reliable method of melanoma diagnosis. In 1994, Nachbar et al. (38) studied on the accuracy of the ABCD rule resulting that specificity was about 90% and sensitivity was around 92%.

The ABCD rule represents the second step of a two-step algorithm. (6) First, pigmented skin lesion will be classified as melanocytic or non-melanocytic. When melanocytic lesion is diagnosed, this calculated rule will be applied.

For the ABCD rule calculation will be scored and interpreted according to *Table 2.2.2.1.1a*.

Table 2.2.2.1.1a ABCD rule of dermoscopy (Modified 1994) (38)

Criteria	**Description**	**Score**	**Weight factor**
Asymmetry	Assess both colors and structures of horizontal and vertical axes	0-2	1.3
Borders	Abrupt ending of pigment pattern at the periphery in 0-8 segments (all axes)	0-8	0.1
Colors	Presence of up to six colors white, red, light-brown, dark brown, blue-gray, and black)	1-6	0.5
Differential structures	Presence of network, structureless or homogeneous areas, streaks, dots, and globules	1-5	0.5
Total Dermoscopy Score(TDS)	**Interpretation**		
<4.75	Benign melanocytic lesion		

4.8-5.45	Suspicious lesion; close follow-up or excision recommended
>5.45	Highly suspicious lesion for melanoma

Formula for calculating TDS:

[(A score x 1.3) + (B score x 0.1) + (C score x 0.5) + (D score x 0.5)]

The 7-point checklist was studied to evaluate the seven features which were frequently associated with histopathologic examination of melanoma.

To diagnose melanoma using this approach, the criteria either 1 major plus 1 minor or 3 minor criteria is required. (see *Table 2.2.2.1.1b*).

Table 2.2.2.1.1b The 7-point checklist. A minimum total score of 3 is required for the diagnosis of melanoma (6)

Criteria	**Score**
Major criteria: 1. Atypical pigment network	2
2. Blue-whitish veil	2
3. Atypical vascular pattern	2
Minor criteria: 4. Irregular streaks	1
5. Irregular pigmentation	1
6. Irregular dots/globules	1
7. Regression structures	1

The Menzies' method is an approach based on the recognition of two negative dermoscopic features and nine positive features seen in *Table*

2.2.2.1.1d. For melanoma diagnosis, a lesion must neither have negative feature and must have at least one out of nine positive features.

Table 2.2.2.1.1c Menzies' method for the diagnosis of melanoma. (6)

	Criteria
Negative features	Symmetry of pattern
	Presence of a single color
Positive features	1.Blue-white veil
	2.Multiple brown dots
	3.Pseudopods
	4. Radial streaming
	5. Scar-like depigmentation
	6. Peripheral black dots/globules
	7. Multiple (5-6) colors
	8. Multiple blue/gray dots
	9. Broadened network

(2) The analytical approach is based on the Chaos & Clues method. First, pigmented skin lesion must be thoroughly decided whether chaotic or not based on its color and pattern in both horizontal and vertical axes. If the lesion is not chaotic, there is no further intervention. In the other hand, if the lesion is chaotic, you must look for a clue in the diagnosis of melanoma which is shown in *Figure 2.2.2.1.2*. If the lesion has at least one of the clues, biopsy might be considered. (33)

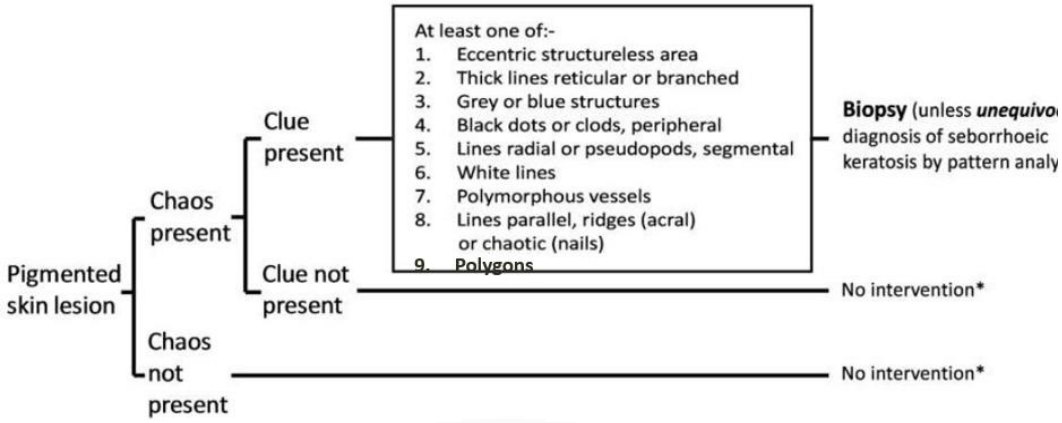


Figure 2.2.2.1.2 The analytical approach (Chaos & Clues method) (33)

From two main approaches of dermoscopic images, we can conclude that the main principles are based on colors and structures. However, dermoscopic features vary between lesions from different sites of body, with particular locations such as face, nails, palms and soles, and mucous membranes have unique pigmentation patterns. (4)

In literature reviews, the sensitivity of melanoma diagnosis increased by 20% and the specificity increased by 10% when using dermoscopy compared to the naked eyes examination. There was no significantly different between their overall performance of different algorithms. (39) However, due to the complexity of features and patterns, the accuracy in diagnosis using dermoscopic examination has limitations especially for inexperienced dermatologists. (40, 41) The diagnostic accuracy of dermoscopy is even worse in general practitioners. (42) The sensitivity using dermoscopy for melanoma diagnosis is approximatedly 80%-90%, based on the experience of the dermatologists. The specificity of this method were up to 90% for the experts, while general practitioners drop into 62%-63%. (25, 26, 31, 41)

2.2.3 Histopathological examination

Histopathological examination is the gold standard for pigmented skin lesions diagnosis and staging in many guidelines (11, 16, 43, 44), although the rate of discordant readings between pathologists can be high. Up to 50% discordance rate among pathologists has been reported. (45, 46) Thus, the diagnostic accuracy of melanoma remains problematic independent of the method used for diagnosis.

2.3 Computer aided diagnosis in skin cancers

Computer aided detection (CAD) and computer aided diagnosis (CADx) software are important tools in different fields of medical imaging for diagnosis and evaluation. These technologies may assist physicians to gain "second opinion" to their diagnoses. In clinical situation, automated system has been widely applied in detection of lesions such as lung tumor on chest x-ray or CT scans (47), polyp or tumor detection in CT colonography(48), and breast lesion detection in mammography. (49, 50) Computer aided diagnosis has also been used to analyze skin lesions and other diagnostic images. (51, 52) In dermatologic field, the practical value of the integration of this advanced computer into pigmented skin lesions diagnosis for dermatologists still needs further investigations and validations. (41, 42, 53-55)

Due to low diagnostic accuracy of malignant melanomas in non-specialized physicians, the scarcity of well-trained dermatologists, limitation in diagnosis of early melanoma, and acknowledge that a dermatologist's clinical approaches and diagnosis are based on morphologic factors such as color, shape etc. beyond dermoscopic inspection of a lesion, have led many institutes worldwide to develop the automated diagnostic tool for melanoma screening.

The development of computational methods helps general physicians as well as dermatologists to give faster and more accurate diagnoses. After several successful studies on computer aided diagnosis for melanoma (56-60), the better algorithms have been developed every year. Recent developments in artificial intelligence called deep learning have raised expectations for the researchers all over the world that fully automated diagnostic software will become available to detect skin cancers especially malignant melanoma without human expertise. (25, 61, 62)

Most of automated systems for screening of melanoma are programed to imitate the decision making by the dermatologist when approaching pigmented skin lesion images. They were primarily developed to gain better performances especially in specificity and sensitivity in melanoma diagnosis when compared to Board-certified dermatologists. Although the software is being processed for various imaging modalities, two main approaches are clinical photography and dermoscopic images. (3, 25, 42, 58, 59, 63-65)

General principle of CAD and CADx system are based on four steps. First, image preprocessing techniques are used to locate the lesions and allows reducing various artifacts like hairs, air bubbles, ruler markings etc. presented in the images. Then, it focuses on the lesion by using image segmentation method. When the lesion is located, different shape, texture, color and other morphological features will be extracted and used to process in classification as the last step.

These following lists are the CAD steps to help in diagnosis of pigmented skin lesions. (*Figure 2.3*) (25)

1. Image preprocessing
2. Image segmentation
3. Feature extraction
4. Classification

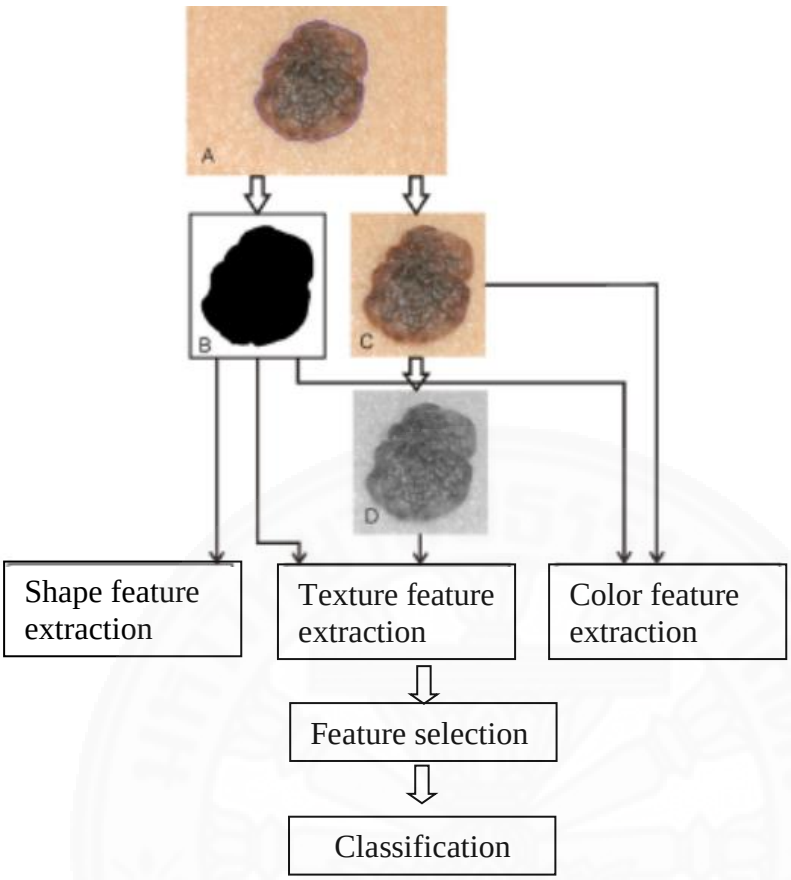


Figure 2.3 CAD steps to help in diagnosis of pigmented skin lesions

Recently, there have been over hundreds of research studied on dermoscopy and automated computational system in diagnosis of pigmented skin lesions. Many approaches to these topics have been proposed to reach higher diagnosis performances. (66) For examples

- Mathematical features for the border evaluation of pigmented skin lesion images.
- New different approaches in melanoma segmentation including color clustering, wavelet analysis, Markov tree features etc.
- Several developed classifiers

Numerous studies have developed more effective CADx systems that can distinguish benign versus malignant pigmented skin lesions by utilizing digital dermoscopic images with high diagnostic performances almost the same level to dermatologists. (67-71) Comparing performances among different systems is difficult

because the outcomes were depending to the specific data set used for each experiment. Also, other reasons such as different features and image sets, different classifier parameters and different learning procedures make it difficult to compare among different algorithms. A major problem which occurred in most systems and researches is the lack of publicly available databases of dermoscopic images to train algorithm.

In conclusion, the clinical value of automated dermoscopic image classifying systems is currently needed further investigations. (67)

2.3.1 Artificial intelligence

According to the Oxford Living Dictionary, the term artificial intelligence (AI) means "the theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making and translation between languages."

Early AI research in the 1940s explored issues about programmable digital computer for mathematical problems. (72) The field of AI research was founded in 1956 in Dartmouth College. Later, the US Department of Defense applied this type of work and started training computers to mimic basic human reasoning. Investment and interest in AI were significantly increased in the first decades of 21st century, when it was successfully integrated to many problems in both educational and industrial fields. (73)

AI system is the software which be able to gather input data with quick processing approaches, then allowing the system to learn automatically from patterns or features shown in the dataset and finally solve the problems. AI is a field of study that integrates many basic knowledge principles, methods, experiments, and technologies, as well as the following major subfields listed below.

- **Machine learning** is an automatedly analyzing model. It applies methods from neuronal model to search automatically for hidden data without being programmed from humans.
- **A neural network** is one of machine learning that contains of millions of dots connected together like neuronal model in human's brain. It processes data by correlating data between each

dot. The method needs several passes and layers at the data to line up the connections and deliver the answer.

- **Deep learning** uses large neural networks with multiple layers of processing units. It can deal with large amount of data and solves many difficult tasks. Common applications with evidence of high performances include image and speech recognition.

2.3.3 Deep learning

Deep learning (DL) was developed in 1980s from the traditional neural network paradigm of artificial intelligence which mimicked model of neurons in the brain. (74) Today, the most useful neural network models are composed of thousands of multi-layered artificial neurons that are parameterized by exponentially more biases and weights that require massive datasets to estimate. However, once these networks are trained on sufficiently large high quality labeled datasets, they generally outperform other machine learning methods. The keyword of deep learning is that multiple layers in processing method are not programed by human beings, they are learned from data. (75) Furthermore, the exponential growth in computational power and the recent emergence of GPU computation, together with the abundance of large data sets to train on makes deep learning application more practical now than ever before.

Deep learning has received high attention during recent years for their capability to convert large amount of information into highly thinking procedures which mimic human's brain using machine learning methods. Recently, this neural network has been used in several fields, e.g., speech recognition, face recognition, object classification, and medical screening, due to outperformance over other machine learning algorithms. (76) Such attention has been growing in the field of medical image detection and diagnosis, particularly in pigmented skin lesions all over the world. (25, 61, 62, 65, 77-79)

In 2015, Google developed AI called AlphaGo to beat World champion human Go player using deep learning. Also, deep convolutional neural networks (CNNs) which are technique in deep learning, showed high potential for processing in many difficult tasks especially fine-grained object categories task which

can benefit in classification of skin lesion appearances like in the work by Esteva et al. (80) which demonstrated that AI was able to classify skin cancers with the same level as experienced dermatologists.

Recently, a group of Thai researchers from Chulalongkorn university and Thammasat university, has trained AI with four high potential algorithms in classification of melanomas, nevi, and seborrheic keratoses (see *Figure 2.3.2a*) by using dermoscopic images from International Skin Imaging Collaboration (ISIC) Challenge 2017 dataset. (see *Figure 2.3.2b*)

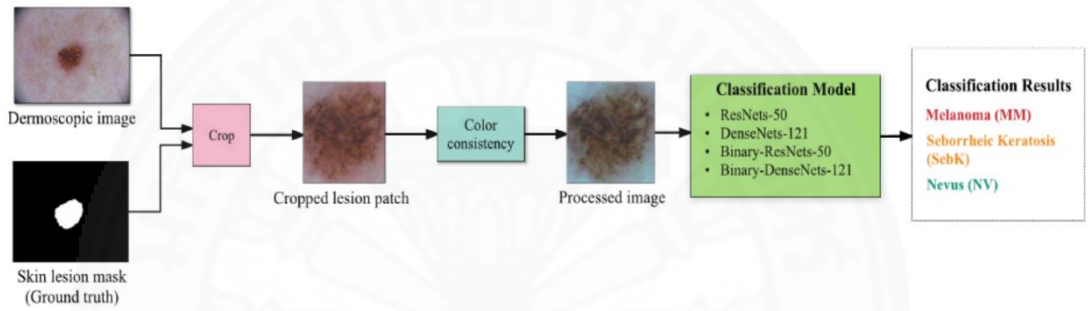


Figure 2.3.2a Flowchart of algorithms used to classify melanoma, seborrheic keratosis, and nevus.

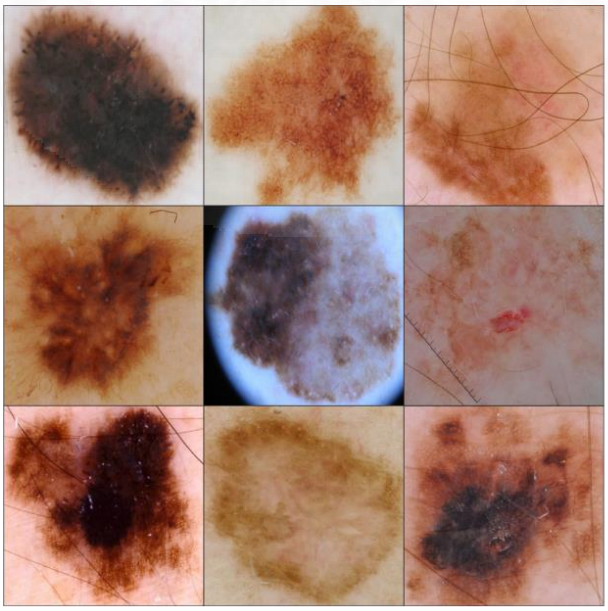


Figure 2.3.2b Dermoscopic images of malignant melanoma from ISIC-ISBI Challenge 2017. Available from http://isic-archive.com/

Four algorithms in classification process included Densely Convolutional Network (DenseNets- 121), Binary-DenseNets-121, Deep residual neural networks (ResNets-50), and Binary-ResNets-50.

(1) Convolutional Neural Networks (CNNs)

Convolutional Neural Networks (CNNs) have been used mainly for visual recognition propose. (81) These networks are technique in deep learning (82) that can extract features with deeper networks automatically during training.

(2) Deep Residual Neural Networks (ResNets)

ResNet is a type of CNN that inserts shortcut connections as extra layers, which turn the network into its counterpart residual version. It bypasses signal from one layer to the other layer via identity connections. This network can be used when the input and output are in the same dimension. (83) (see *Figure 2.3.2c*)

(3) Densely Convolutional Network (DenseNet)

Densely Convolutional Network (DenseNet) is a network that directly connects each layer to the other layers in the network in a feed forward manner. (see *Figure 2.3.2d*) DenseNets can solve the vanishing gradient problem, reuse feature, and reduce the number of parameters. (81) Moreover, DenseNets connection helps to reduce overfitting of model with limited training dataset.

(4) Binary classifiers

Binary classifiers are techniques to filter each classification into two classes for examples MM vs. rest, SebK vs. rest, NV vs. rest. (see *Figure 2.3.2e*)

Figure 2.3.2c Example network architectures for CNNs. Right : a residual network with 34 parameter layers. (83)

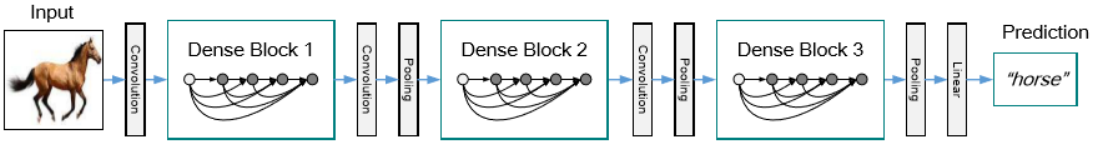


Figure 2.3.2d A deep DenseNet with three dense blocks (81)

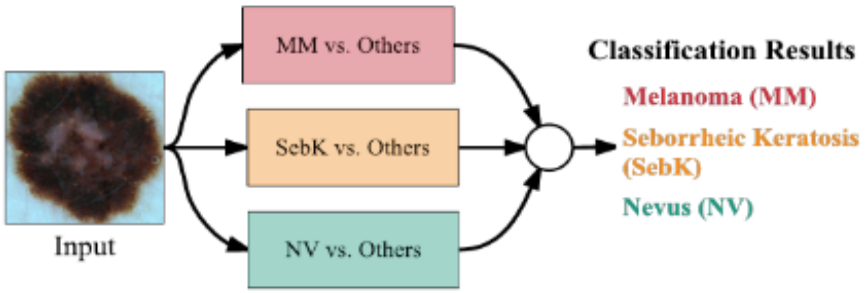


Figure 2.3.2e Diagram of 3-Binary DenseNet121 classifier and 3-Binary ResNet50 classifier. The results are based on weighted vote accuracy from each sub classifier. (84)

The result showed that DenseNet-121, one of four deep learning algorithm network which directly connects each layer to the other layers in the network, performed the best in sensitivity, specificity, and accuracy up to 80-90%. (84) (see Figure 2.3.2f and *Table 2.3.2*) Moreover, with the help of artificial training images generated from integration of Generative Adversarial Networks (GANs), a powerful form of generative model which can approximately sample from high dimensional distributions like natural images, can solve the problem of scarcity of training data and improve classification outcome of melanoma.

Table 2.3.2 Area under ROC curve of different methods on diagnosis of melanoma, nevus, and seborrheic keratosis

Algorithm models	**% Average AUC ± SD**		
	Melanoma	**Nevus**	**Seborrheic keratosis**
DenseNets-121	82.96 ± 1.23	86.91 ± 0.98	93.62 ± 0.68
Binary-DenseNets-121	82.82 ±5.49	85.90 ±1.48	92.94 ±1.07
ResNets-50	80.24 ± 2.49	84.91 ± 0.87	91.17 ± 0.95
Binary-ResNets-50	80.07 ±6.11	85.56 ±1.77	91.87 ±1.23

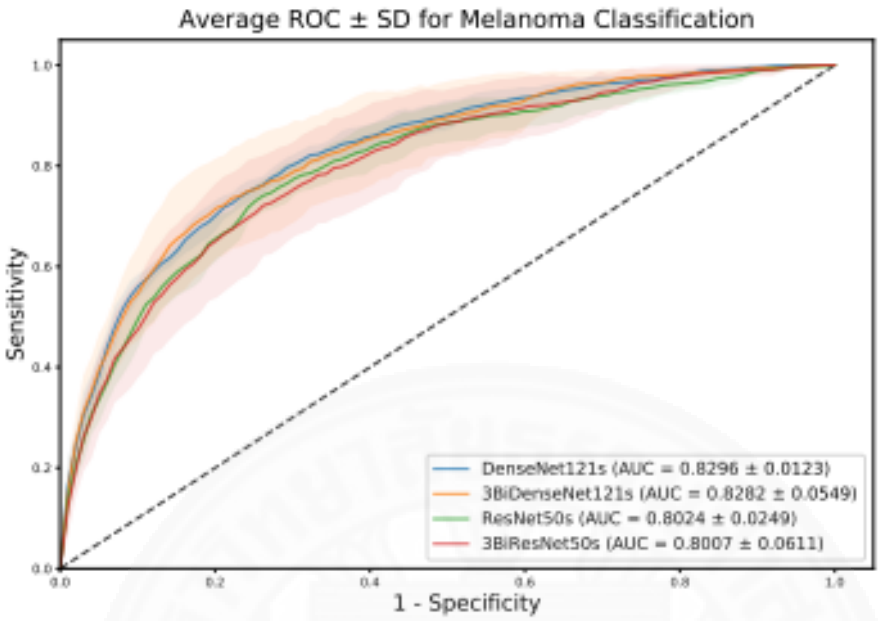


Figure 2.3.2f Average ROC ± SD of four algorithms and the average AUC ± SD for melanoma (MM) classification

From the successful improvement of automated melanoma recognition using DenseNet algorithm, they have explored further on other skin cancers to be proved on diagnostic performance.

Although AI system had impressive results under the experimental conditions, dermoscopic images used to train and assess effectiveness from previous study were based on the ISIC-ISBI challegnge 2017. The researchers doubt whether AI can classify the real clinical dermoscopic images in Asian patients or not.

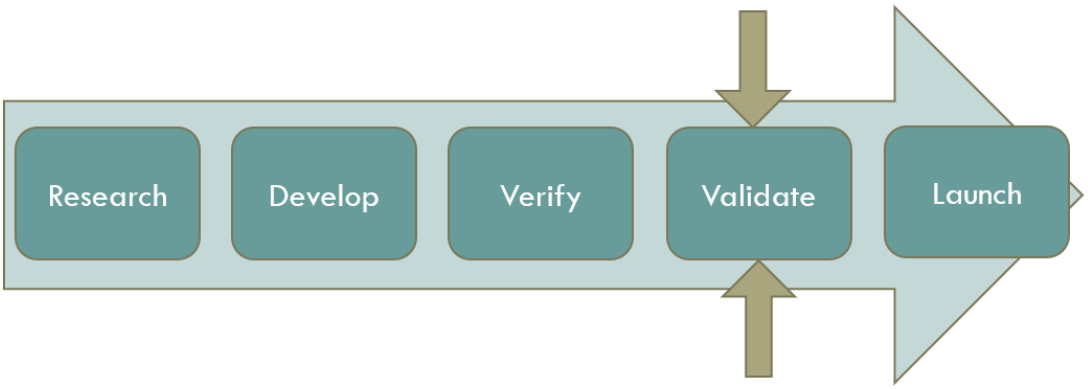


Figure 2.3.2g Flowchart of scientific development design in this study

This flowchart shows overall view of our project. In this study, we aimed to validate the diagnostic performances of the first artificial intelligence assisted skin cancer screening system in Thailand and compare the diagnostic ability to Board-certified dermatologists and experienced dermoscopic specialized dermatologists using clinical dermoscopic images.

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Materials

3.1.1 Dermoscopic images of pigmented skin lesions

3.1.1.1 Test dataset

(1) Sample size

Clinical dermoscopic images of pigmented skin lesions including Melanoma, Squamous cell carcinoma, Basal cell carcinoma, Seborrheic keratosis, Nevus, and other skin lesions from the medical records in Samitivej Sukhumvit Hospital, Bangkok, Thailand from January 2014 to December 2017. All lesions were biopsied for histopathological examination to confirm diagnosis. All images were taken with FotoFinder Hub® system (FotoFinder Systems GmbH, Deutschland) and were saved in JPG format.

Sample Size determination

The sample size was calculated from the formula of Testing for one population proportion formula

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 p(1-p)}{\epsilon^2}$$

$$\epsilon = p - p_0$$

Reference value (p_0) = 1

Proportion (p) = 0.95

$\alpha = 0.05$

$\beta = 0.1$

Sample size(n) = 200

(2) Inclusion criteria

2.1) Dermoscopic images of pigmented skin lesions including Melanoma, Squamous cell carcinoma, Basal cell carcinoma, Seborrheic keratosis, Nevus, and other skin lesions from the medical records in Samitivej Sukhumvit Hospital, Bangkok, Thailand from January 2014 to December 2017

2.2) All images must be confirmed diagnosis by histopathological examination

(3) Exclusion criteria

3.1) Inadequate image qualities: poor focus, too much artifacts

3.2) Images which are included multiple lesions

3.3) Images which lesions encompassed the entire field of view

3.4) Images with non-histopathological examined lesions

3.5) Images which exists in trained dataset for AI

3.1.1.2 Trained dataset

(1) Study population

Dermoscopic images of pigmented skin lesions including Malignant melanoma (MM), Squamous cell carcinoma (SCC), Basal cell carcinoma (BCC), Seborrheic keratosis (SK), and Nevus (NV) used to train and access effectiveness of artificial intelligence system in this study were based on four sources as listed below. (see *Table 3.1.1.2*)

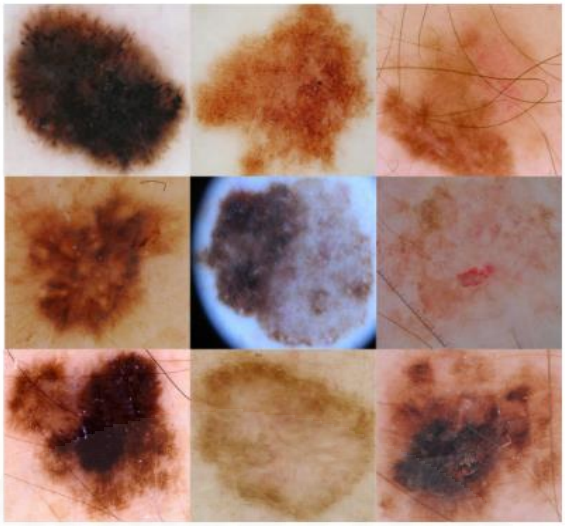
1) ISIC-ISBI Challenge 2017: 2000 images; melanoma 374 images, nevus 1372 images, seborrheic keratosis 254 images
2) Medical records in Samitivej Sukhumvit Hospital, Bangkok, Thailand from January 2014 to December 2017: 82 images; melanoma 25 images, seborrheic keratosis 52 images, SCC 3 images, and BCC 2 images
3) Medical textbooks: 269 images; melanoma 217 images, seborrheic keratosis 40 images, SCC 8 images, and BCC 4 images
    - Dermatoscopy in clinical practice second edition
    - Dermoscopy: an illustrated self-assessment guide
    - Compendium of surface microscopic and dermoscopic features
    - Handbook of dermoscopy

4) Journal articles: 120 images; SCC 18 images and BCC 102 images

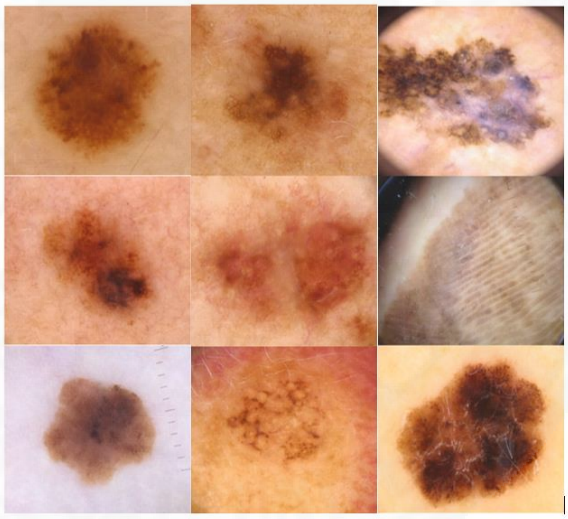
Table 3.1.1.2 Sources of trained dataset

TRAINED DATASET	MM	SK	NV	BCC	SCC
ISIC 2017	374	254	1372	-	-
Smitivej hospital	25	-	-	22	3
Textbooks	217	40	-	47	8
Journal articles	-	-	-	102	18
Total	616	346	1372	171	29

MM: Melanoma, SK: Seborrheic keratosis, NV: Nevus, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma



a)



b)

Figure 3.1.1a and 3.1.1b Examples of dermoscopic images of melanoma

a) From ISIC-ISBI Challenge 2017

b) From medical records in Samitivej Sukhumvit Hospital; images were taken with FotoFinder Hub® system

Figure 3.1.1c FotoFinder Hub® system (FotoFinder Systems GmbH, Deutschland)

3.2 Research design

Retrospective, descriptive study

3.2.1 Study location

Skin and laser clinic at Samitivej Sukhumvit Hospital, Bangkok, Thailand

3.2.2 Study procedures

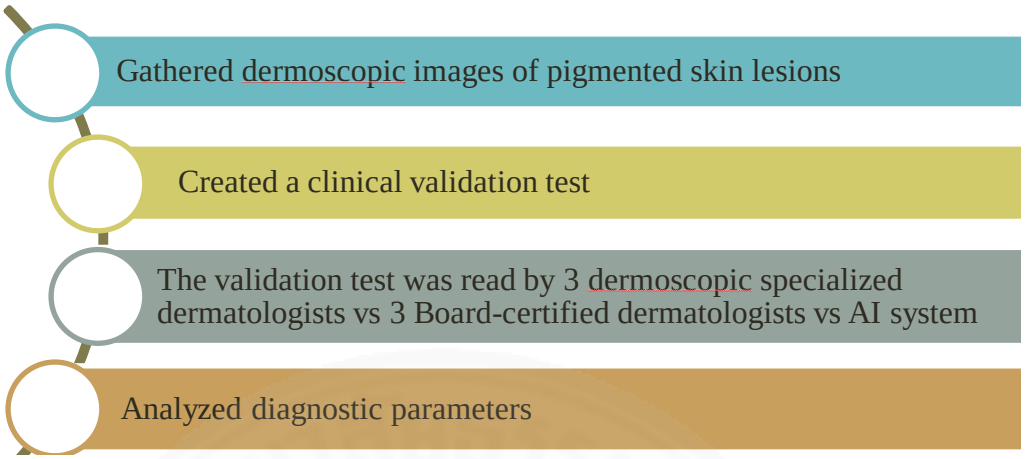


Figure 3.2.2 Flow chart of study procedures

3.2.2.1 This study was approved by Institutional Review Board of Bangkok Hospital Medical Center (BMC-IRB) before starting the experiment.

3.2.2.2 Gathered clinical dermoscopic images of pigmented skin lesions including Melanomas, Basal cell carcinomas, Squamous cell carcinomas, Seborrheic keratoses, and Nevi from the medical records in Samitivej Sukhumvit Hospital from January 2014 to December 2017. All lesions were biopsied for histopathological examination to confirm diagnosis.

Data collection

(1) Genders

(2) Ages

(3) Dermoscopic images of lesions

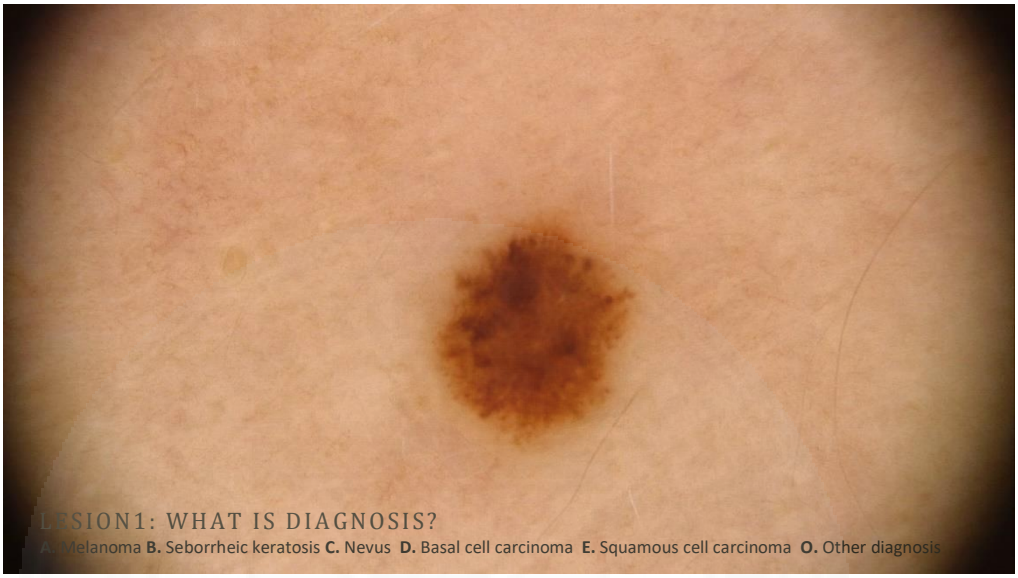
(4) Locations of lesions

(5) Diagnosis of pigmented skin lesions

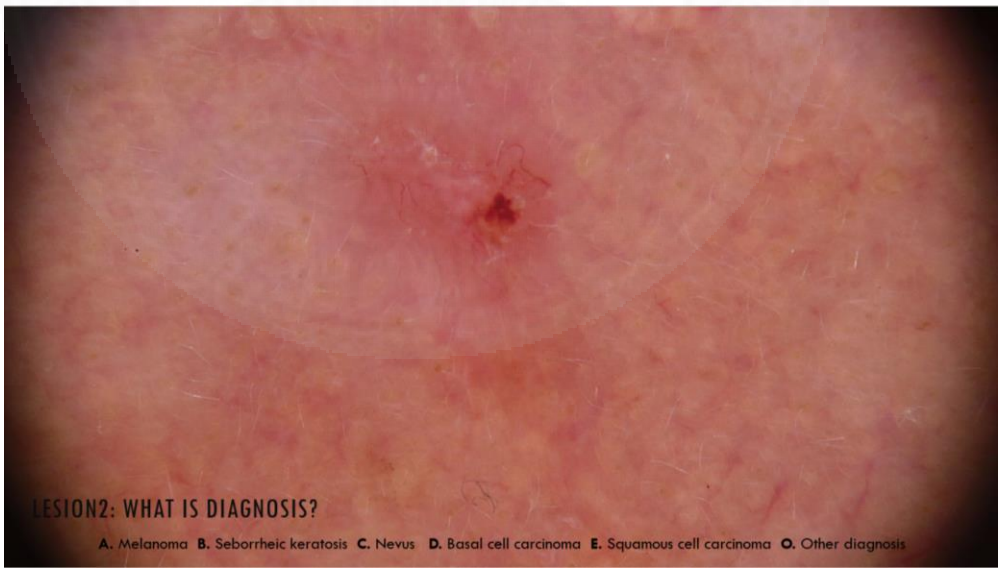
(6) Histopathological examination from skin biopsies

3.2.2.3 Created the validation test using randomly computerized selected 200 clinical dermoscopic images including 31 melanomas, 39 basal cell carcinomas, 6 squamous cell carcinomas, 52 seborrheic keratoses, 65 nevi, and 7 other lesions including 2 cherry hemangiomas, 2 telangiectasias, tattoo, dermatofibroma, and clear cell acanthoma.

Each dermoscopic image was provided one correct answer out of six choices; melanoma, basal cell carcinoma, squamous cell carcinoma, seborrheic keratosis, nevus, and other diagnosis.



a)



b)

Figure 3.2.2.3a,b Examples of validation test for dermatologists

3.2.2.4 This validation test was read by three Board-certified dermatologists versus three dermoscopic specialized dermatologists versus artificial intelligence system (Deep learning).

All readers were blinded to the diagnosis and clinical images. No additional clinical information was given to the dermatologists. No time restrictions. All readers could complete the test over multiple sittings.

3.2.2.5 Analyzed diagnostic parameters of each type of pigmented skin lesions among three groups.

3.2.3 Outcome measurements

3.2.3.1 Sensitivity for diagnosis each type of pigmented skin lesions

3.2.3.2 Specificity for diagnosis each type of pigmented skin lesions

3.2.3.3 Accuracy for diagnosis each type of pigmented skin lesions

3.2.3.4 Positive predictive value (PPV) for diagnosis each type of pigmented skin lesions

3.2.3.5 Negative predictive value (NPV) for diagnosis each type of pigmented skin lesions

3.2.3.6 Compare diagnostic performances among three groups: Board-certified dermatologists versus dermoscopic specialized dermatologists versus artificial intelligence system (Deep learning).

3.3 Data analysis

3.3.1 Diagnostic performance analysis

The primary outcomes were diagnostic performances of three groups on each type of pigmented skin lesions including sensitivity, specificity, accuracy, positive predictive values, and negative predictive values. The values were calculated in percentage (%) based on the following standard formulae.

3.3.1.1 Sensitivity for diagnosis each type of pigmented skin lesions

$$\text{Sensitivity} = \frac{TP}{TP + FN}$$

3.3.1.2 Specificity for diagnosis each type of pigmented skin lesions

$$\text{Specificity} = \frac{TN}{TN + FP}$$

3.3.1.3 Accuracy for diagnosis each type of pigmented skin lesions

$$\text{Accuracy} = \frac{(TP + TN)}{(TP + TN + FP + FN)}$$

3.3.1.4 Positive predictive values for diagnosis each type of pigmented skin lesions

$$\text{Positive predictive values} = \frac{TP}{TP + FP}$$

3.3.1.5 Negative predictive values for diagnosis each type of pigmented skin lesions

$$\text{Negative predictive values} = \frac{TN}{TN + FN}$$

		Condition (as determined by "Gold standard")			
	Total population	Condition positive	Condition negative	Prevalence = Σ Condition positive / Σ Total population	
Test outcome	Test outcome positive	True positive	False positive (Type I error)	Positive predictive value (PPV, Precision) = Σ True positive / Σ Test outcome positive	False discovery rate (FDR) = Σ False positive / Σ Test outcome positive
	Test outcome negative	False negative (Type II error)	True negative	False omission rate (FOR) = Σ False negative / Σ Test outcome negative	Negative predictive value (NPV) = Σ True negative / Σ Test outcome negative
	Positive likelihood ratio (LR+) = TPR/FPR	True positive rate (TPR, Sensitivity, Recall) = Σ True positive / Σ Condition positive	False positive rate (FPR, Fall-out) = Σ False positive / Σ Condition negative	Accuracy (ACC) = Σ True positive + Σ True negative / Σ Total population	
	Negative likelihood ratio (LR−) = FNR/TNR	False negative rate (FNR) = Σ False negative / Σ Condition positive	True negative rate (TNR, Specificity, SPC) = Σ True negative / Σ Condition negative		
	Diagnostic odds ratio (DOR) = LR+/LR−				

Figure 3.3.1 Diagnostic parameters (85)

When evaluate the group values from several readers in the same group, the mean values of each diagnostic parameters were used in our analysis.

The secondary outcomes were comparison among three groups on diagnostic performances of each type of pigmented skin lesions.

3.3.2 Statistical analysis

Artificial intelligence system (Deep learning) submitted predictions of each dermoscopic image with one out of six choices including 0, 1, 2, 3, 4, 5. Also, all dermatologists submitted predictions of each image with one out of six choices including A, B, C, D, E, O.

Each score was checked 6 times with correct (1.0) and incorrect (0.0) answer in each choice.

Kappa analysis and Interclass correlation coefficient (ICC) were used to evaluate readers' performance correlation among each dermatologist group.

In all graphs, the baseline value is 0.00. Statistical analyses used SPSS (version 10.0).

CHAPTER 4
RESULTS AND DISCUSSION

4.1 Results

4.1.1 Diagnostic performances of each type of pigmented skin lesions

4.1.1.1 Board-certified dermatologists

Table 4.1.1.1 Mean diagnostic performances of Board-certified dermatologists in diagnosis of different pigmented skin lesions

	MM	BCC	SCC	SK	NV	Others
Sensitivity (%)	22.6	42.7	16.7	63.5	31.8	95.2
Specificity (%)	93.7	97.1	94.0	82.5	92.3	75.6
Accuracy (%)	82.7	86.5	91.7	77.5	72.7	76.3
PPV (%)	42.0	79.2	9.9	58.6	64.3	12.8
NPV (%)	86.9	87.5	97.3	86.1	74.2	99.8

MM: Melanoma, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, SK: Seborrheic keratosis, NV: Nevus, Others: Other diagnosis

From *Table 4.1.1.1*, mean sensitivities of Board- certified dermatologists in melanoma, BCC, and SCC diagnosis were 22.6%, 42.7%, and 16.7% respectively. In contrast, mean specificities in diagnosis of melanoma, BCC, and SCC were high as 93.7%, 97.1%, and 94.0% respectively. Mean accuracies were 82.7, 86.5, and 91.7%. Moreover, mean positive predictive values in melanoma, BCC, and SCC diagnosis were 42.0%, 79.2%, and 9.9%. Mean negative predictive values were 86.9%, 87.5%, and 97.3% respectively.

Benign pigmented skin lesions which are seborrheic keratosis, nevus, and other diagnosis, mean sensitivities in diagnosis of Board-certified dermatologists were 63.5%, 31.8%, and 95.2%. Mean specificities in diagnosis in seborrheic keratosis, nevus, and other diagnosis were 82.5%, 92.3%, and 75.6%. Mean accuracies were 77.5, 72.7, and 76.3% respectively. In addition, mean positive predictive values in diagnosis of seborrheic keratosis, nevus, and other pigmented skin

lesions were 58.6%, 64.3%, and 12.8%. Mean negative predictive values were 86.1%, 74.2%, and 99.8% respectively.

Intermediate to excellent agreement beyond each lesion was observed among the readers in this group. (see *Table 4.1.1a*) Also, *figure 4.1.2.1a* shows the good correlation among three dermatologists in diagnosis of different types of skin cancers.

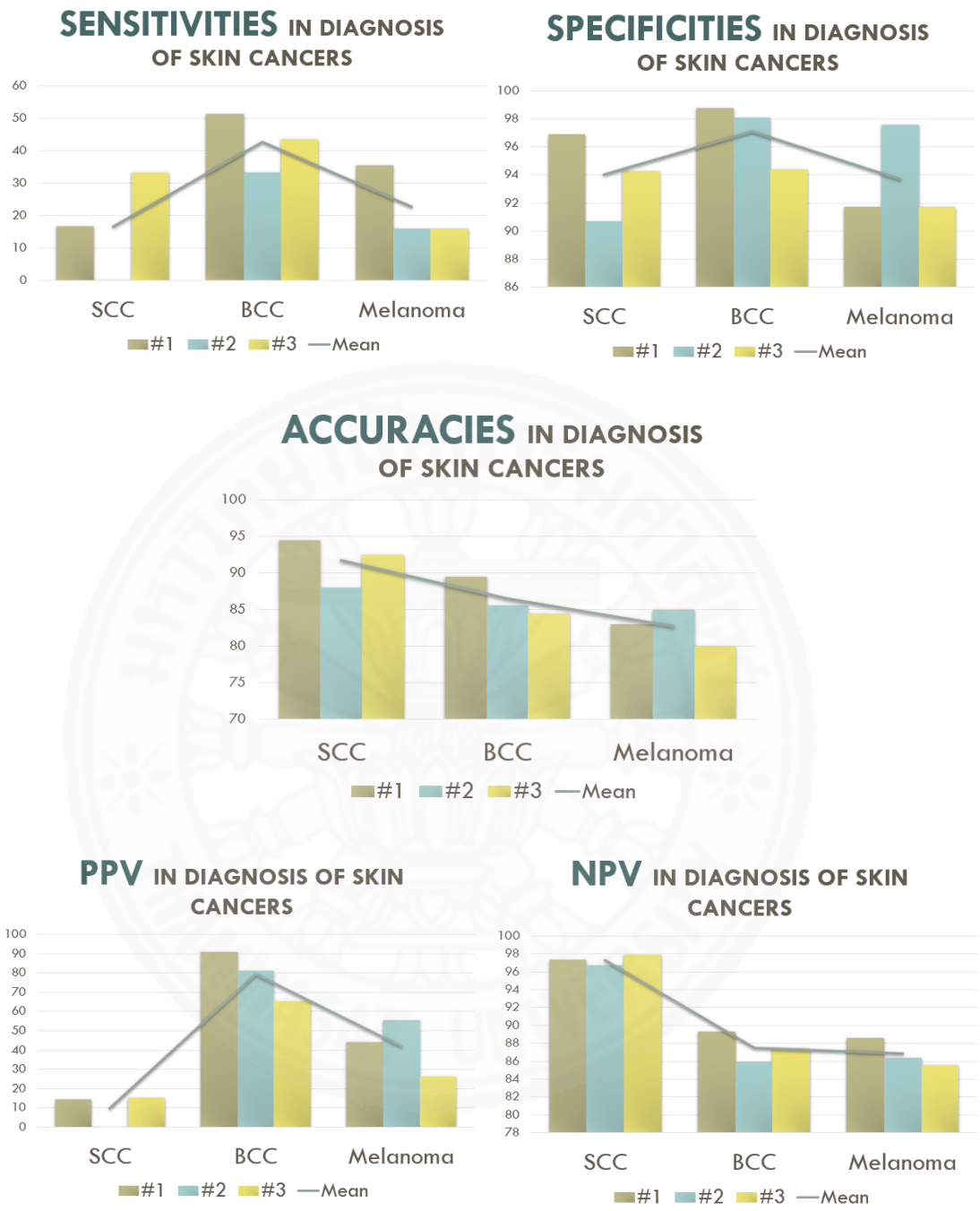


Figure 4.1.2.1a Diagnostic performances in diagnosis of different types of skin cancers; three Board-certified dermatologists and mean values.

4.1.1.2 Experienced dermoscopic specialized dermatologists

Table 4.1.1.2 Mean diagnostic performances of experienced dermoscopic specialized dermatologists in diagnosis of different pigmented skin lesions

	MM	BCC	SCC	SK	NV	Others
Sensitivity (%)	69.9	66.7	72.2	83.3	63.6	90.5
Specificity (%)	82.2	98.2	95.7	97.1	93.6	99.1
Accuracy (%)	80.3	92.0	95.0	93.5	83.8	98.8
PPV (%)	43.5	89.4	38.5	90.9	84.1	80.3
NPV (%)	93.8	92.4	99.1	94.3	84.4	99.7

MM: Melanoma, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, SK: Seborrheic keratosis, NV: Nevus, Others: Other diagnosis

Dermoscopic specialized dermatologists' diagnostic performances were high in almost all parameters.

For skin cancer classification, mean sensitivities in melanoma, BCC, and SCC diagnosis were 69.9%, 66.7%, and 72.2% respectively. Mean specificities in melanoma, BCC, and SCC diagnosis were 82.2%, 98.2%, and 95.7% respectively. Mean accuracies were 80.3, 92.0, and 95.0%. In addition, mean positive predictive values in diagnosis of melanoma, BCC, and SCC were 43.5%, 89.4%, and 38.5%. Mean negative predictive values were 93.8.9%, 92.4%, and 99.1% respectively. (see *Table 4.1.1.2*)

Diagnostic performances in benign pigmented skin lesions showed that mean sensitivities in seborrheic keratosis, nevus, and other lesions were 83.3%, 63.6%, and 90.5%. Mean specificities were 97.1%, 93.6%, and 99.1% respectively. Mean accuracies were 93.5, 83.8, and 98.8%. Moreover, mean positive predictive values in diagnosis of seborrheic keratosis, nevus, and other pigmented skin lesions were 90.9%, 84.1%, and 80.3%. Mean negative predictive values were 94.3%, 84.4%, and 99.7% respectively.

All lesions were classified with excellent agreement among all readers in the group. (see *Table 4.1.1a*) *Figure 4.1.2.2a* also shows the good correlation in skin cancers diagnosis among three dermoscopic specialized dermatologists.

Table 4.1.1a Interclass correlation coefficient (ICC)

	ICC					
	MM	**BCC**	**SCC**	**SK**	**NV**	**Others**
Dermoscopic specialized dermatologists	0.896	0.900	0.868	0.954	0.870	0.936
Dermatologist	0.579	0.846	0.599	0.858	0.718	0.982

MM: Melanoma, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, SK: Seborrheic keratosis, NV: Nevus, Others: Other diagnosis

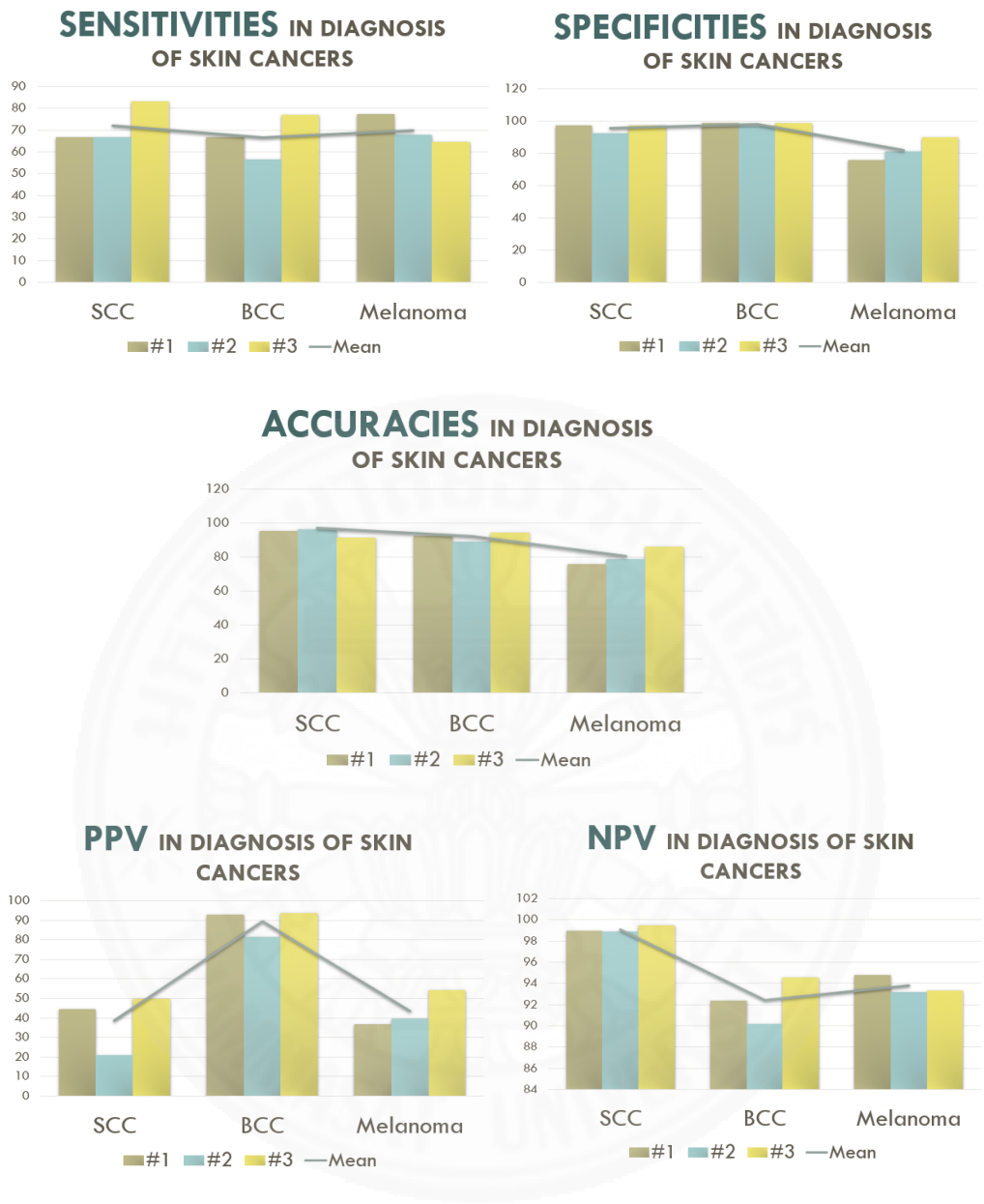


Figure 4.1.2.2a Diagnostic performances in diagnosis of different types of skin cancers; three experienced dermoscopic specialized dermatologists and mean values.

4.1.1.3 Artificial intelligence system (Deep learning)

Table 4.1.1.3 Diagnostic performances of artificial intelligence system in diagnosis of different pigmented skin lesions

	MM	BCC	SCC	SK	NV	Others
Sensitivity (%)	67.7	30.8	16.7	42.3	66.2	57.1
Specificity (%)	69.2	98.8	100	97.3	76.3	88.6
Accuracy (%)	86.0	84.5	95.5	75.5	76.5	87.5
PPV (%)	28.8	85.7	100	84.6	57.3	15.4
NPV (%)	92.1	85.5	97.5	82.8	82.4	98.3

MM: Melanoma, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, SK: Seborrheic keratosis, NV: Nevus, Others: Other diagnosis

Our AI' s diagnostic performances showed sensitivities of 67.7% in melanoma diagnosis, 30.8% in BCC diagnosis, and 16.7% in SCC diagnosis. Specificities of melanoma, BCC, and SCC diagnosis were 69.2%, 98.8%, and 100% respectively. Accuracies were 86.0, 84.5, and 95.5%. Moreover, positive predictive values in melanoma, BCC, and SCC diagnosis were 28.8%, 85.7%, and 100%. Mean negative predictive values were 92.1%, 85.5%, and 97.5% respectively. (see *Table 4.1.1.3*)

For benign pigmented skin lesions, sensitivities in seborrheic keratosis, nevus, and other lesions diagnosis were 42.3%, 66.2%, and 57.1%. Specificities in diagnosis in seborrheic keratosis, nevus, and other diagnosis were 82.5%, 92.3%, and 75.6%. Accuracies were 75.5, 76.5, and 87.5% respectively. In addition, positive predictive values in diagnosis of seborrheic keratosis, nevus, and other pigmented skin lesions were 84.6%, 57.3%, and 15.4%. Negative predictive values were 82.8%, 82.4%, and 98.3% respectively.

Value level	MM	BCC	SCC	NV	SK	Others
MM	21	1	0	9	0	0
BCC	22	12	0	3	2	0
SCC	2	1	1	1	0	1
NV	19	0	0	43	1	2
SK	7	0	0	19	22	4
Others	0	0	0	3	0	4

Predicted level

Figure 4.1.1.3 Confusion matrix of AI system performance

MM: Melanoma, BCC: Basal cell carcinoma, SCC: Squamous cell carcinoma, SK: Seborrheic keratosis, NV: Nevus, Others: Other diagnosis

4.1.2 Comparison of skin cancer diagnostic performances among three groups

4.1.2.1 Sensitivities

In melanoma diagnosis, AI system showed higher sensitivity compared to Board-certified dermatologists (67.7% vs 22.6%) and almost the same level as dermoscopic specialized dermatologists (69.9%).

For BCC diagnosis, AI system had lower sensitivity (30.8%) compared to other groups (Board-certified dermatologist 42.7% vs Dermoscopists 66.7%).

For SCC diagnosis, AI system had lower sensitivity compared to Dermoscopic s specialized dermatologists (16.7% vs 72.2%), but the same level with Board-certified dermatologists (16.7%). (see *Figure 4.1.2.1*)

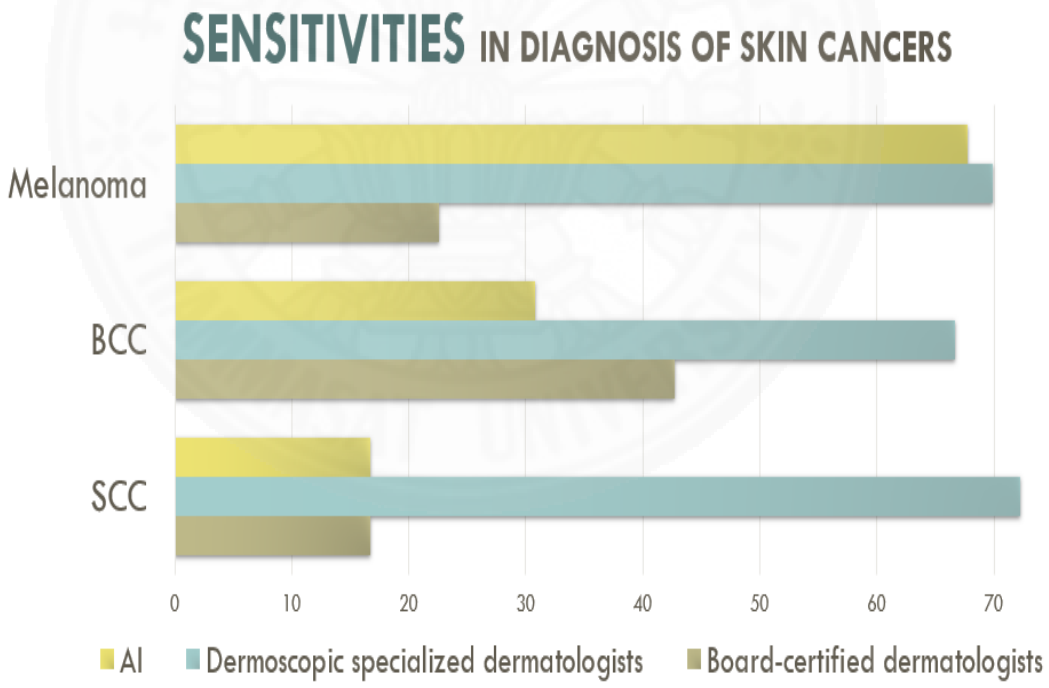


Figure 4.1.2.1 Sensitivities in diagnosis of different types of skin cancers compared among three groups

4.1.2.2 Specificities

Specificities in diagnosis of melanoma, BCC, and SCC among three groups were not significantly different. (see *Figure 4.1.2.2*)

In melanoma diagnosis, specificities of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 69.2%, 93.7%, and 82.2% respectively.

In BCC diagnosis, specificities of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 69.2%, 93.7%, and 82.2% respectively.

In SCC diagnosis, specificities of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 98.8%, 97.1%, and 98.2% respectively. (see *Figure 4.1.2.2*)

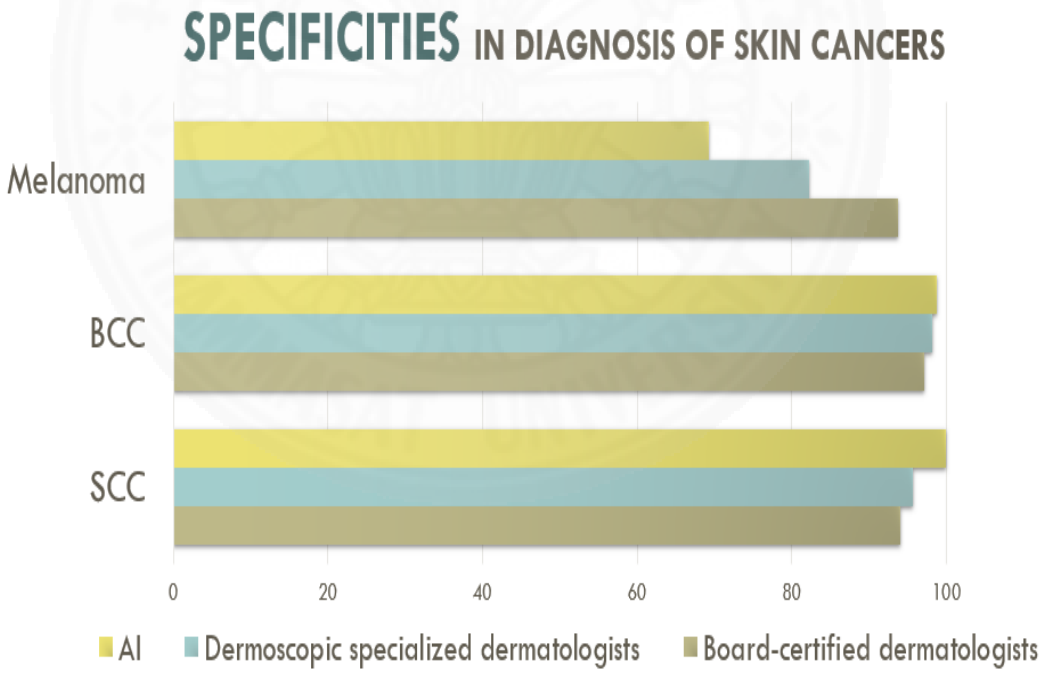


Figure 4.1.2.2 Sensitivities in diagnosis of different types of skin cancers compared among three groups

4.1.2.3 Accuracies

AI system had higher accuracies in diagnosis of melanoma and SCC compared to other groups. (see *Figure 4.1.2.3*)

In melanoma diagnosis, accuracies of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 86.0%, 92.7%, and 80.3% respectively.

For BCC diagnosis, AI system had lower accuracy as 84.5% compared to Board-certified dermatologists as 86.5%, and dermoscopic specialized dermatologists as 92%.

For SCC diagnosis, accuracies of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 95.5%, 91.7%, and 95% respectively.

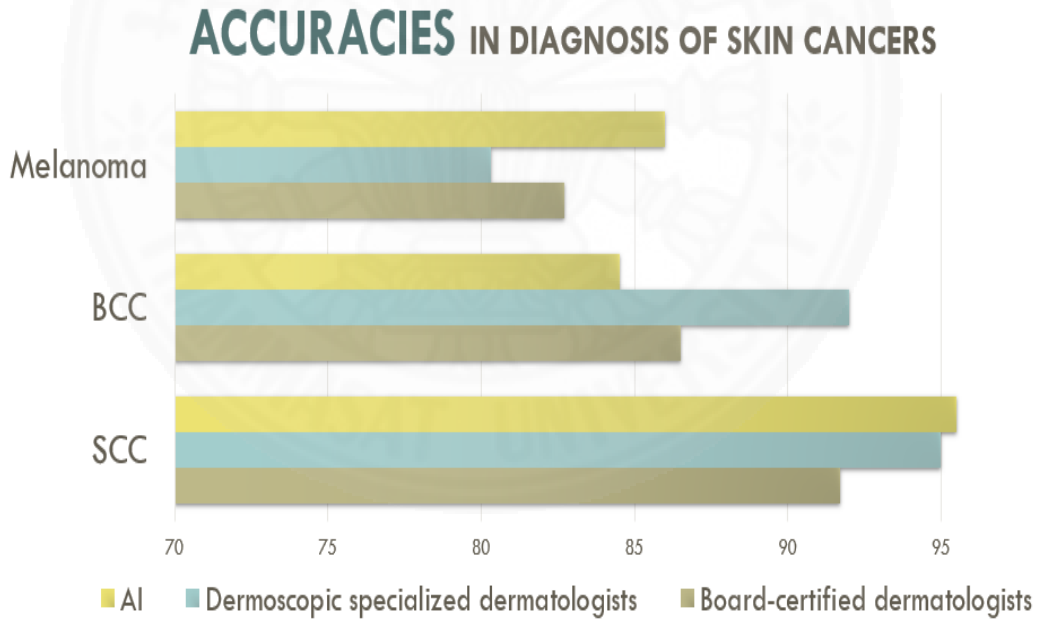


Figure 4.1.2.3 Accuracies in diagnosis of different types of skin cancers compared among three groups

4.1.2.4 Positive predictive values (PPV)

AI system showed higher PPV than other groups in melanoma diagnosis, but lower in BCC diagnosis. (see *Figure 4.1.2.4*)

In melanoma diagnosis, PPV of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 57.9%, 42.0%, and 43.5% respectively.

In BCC diagnosis, PPV of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 58.3%, 79.2%, and 89.4% respectively.

In SCC diagnosis, PPV of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 20.0%, 9.9%, and 38.5% respectively.

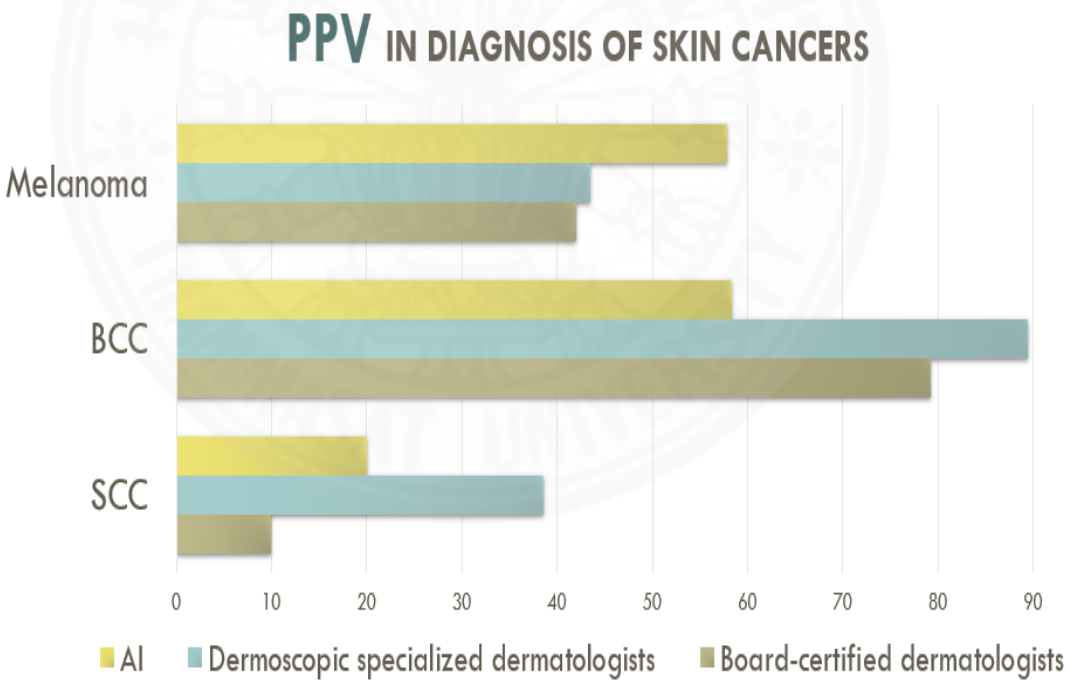


Figure 4.1.2.4 Positive predictive values (PPV) in diagnosis of different types of skin cancers compared among three groups

4.1.2.5 Negative predictive values (NPV)

AI system had higher NPV than other groups in BCC diagnosis. For melanoma and SCC diagnosis, AI system had lower NPV than dermoscopic specialized dermatologists, but higher than Board-certified dermatologists. (see *Figure 4.1.2.5*)

In melanoma diagnosis, NPV of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 89%, 86.9%, and 93.8% respectively.

In BCC diagnosis, NPV of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 92.8%, 87.5%, and 92.4% respectively.

In SCC diagnosis, NPV of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 97.4%, 97.3%, and 99.1% respectively.

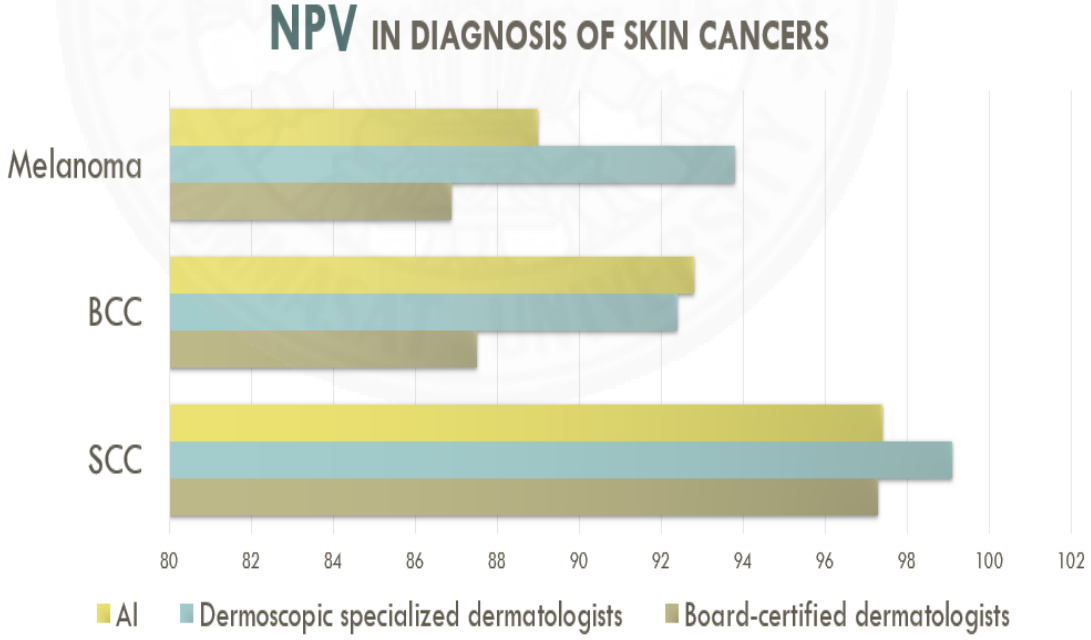


Figure 4.1.2.5 Negative predictive values (NPV) in diagnosis of different types of skin cancers compared among three groups

4.1.3 Comparison of benign pigmented skin lesions diagnostic performances among three groups

4.1.3.1 Sensitivities

AI system had lower sensitivities in seborrheic keratosis and other lesions compared to other groups, in contrast, higher sensitivity in nevus diagnosis. (see *Figure 4.1.3.1*)

In seborrheic keratosis diagnosis, sensitivities of AI system, Board- certified dermatologists, and dermoscopic specialized dermatologists were 26.9%, 63.6%, and 83.3% respectively.

For nevus diagnosis, sensitivities of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 72.3%, 31.8%, and 63.6% respectively.

For other lesions diagnosis, sensitivities of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 57.1%, 95.2%, and 90.5% respectively.

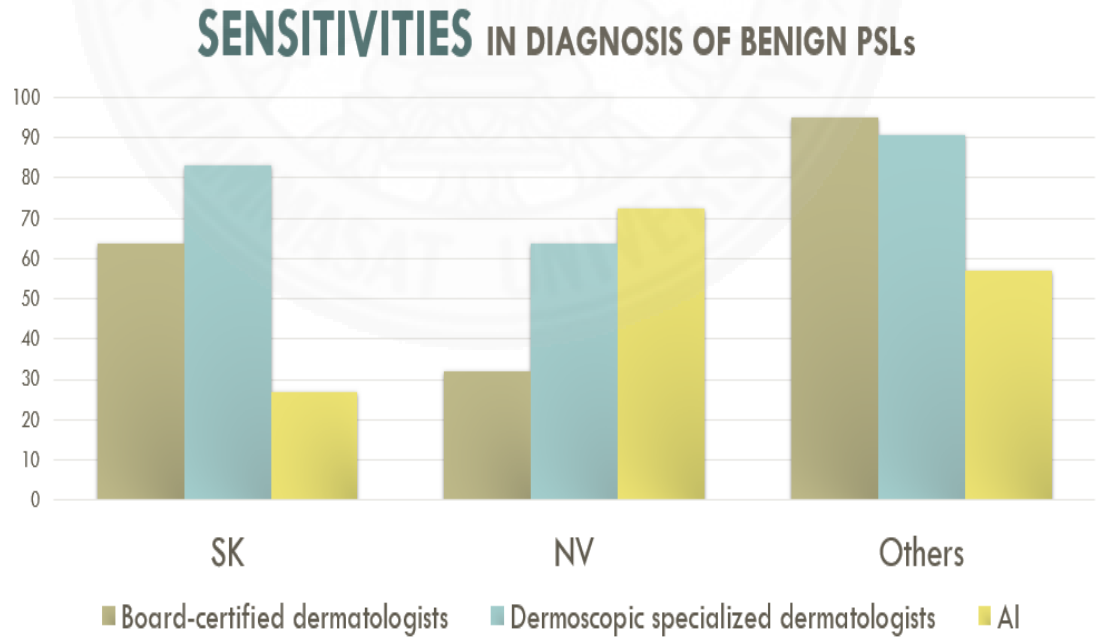


Figure 4.1.3.1 Sensitivities in diagnosis of different types of benign pigmented skin lesions compared among three groups

4.1.3.2 Specificities

Specificities in benign pigmented lesions diagnosis among three groups were similar. (see *Figure 4.1.3.2*)

In seborrheic keratosis diagnosis, specificities of AI system, Board- certified dermatologists, and dermoscopic specialized dermatologists were 92.6%, 82.5%, and 97.1% respectively.

For nevus diagnosis, specificities of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 78.5%, 92.3%, and 93.6% respectively.

For other lesions diagnosis, specificities of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 88.6%, 75.6%, and 99.1% respectively.

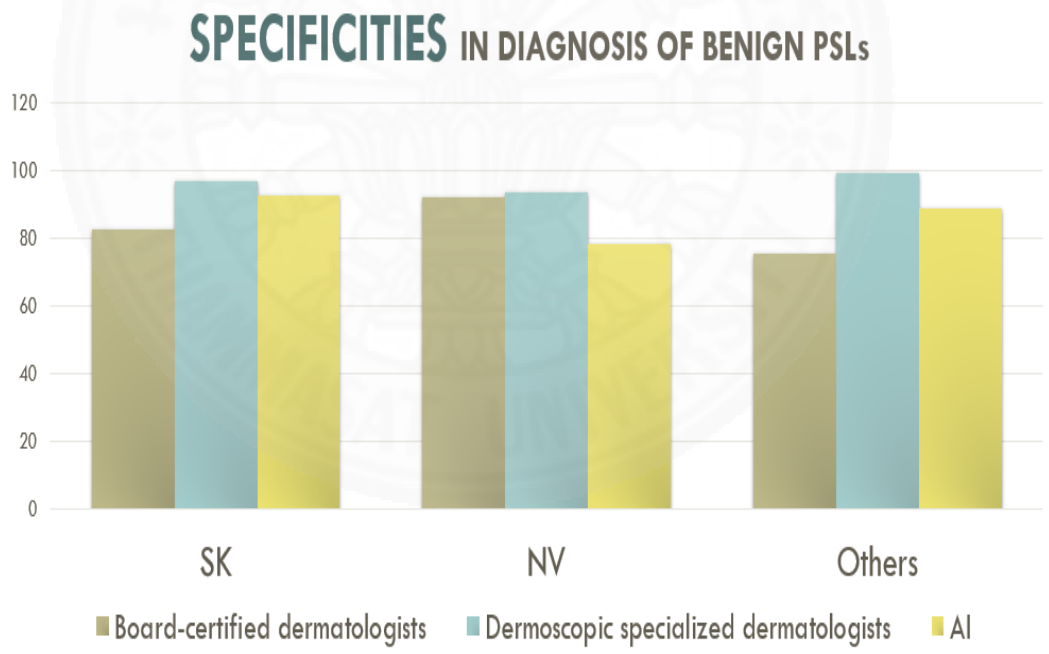


Figure 4.1.3.2 Specificities in diagnosis of different types of benign pigmented skin lesions compared among three groups

4.1.3.3 Accuracies

Accuracies in benign pigmented lesions diagnosis among three groups were similar. (see *Figure 4.1.3.3*)

In seborrheic keratosis diagnosis, accuracies of AI system, Board- certified dermatologists, and dermoscopic specialized dermatologists were 75.5%, 77.5%, and 93.5% respectively.

For nevus diagnosis, accuracies of AI system, Board- certified dermatologists, and dermoscopic specialized dermatologists were 76.5%, 72.7%, and 83.8% respectively.

For other lesions diagnosis, accuracies of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 87.5%, 76.3%, and 98.8% respectively.

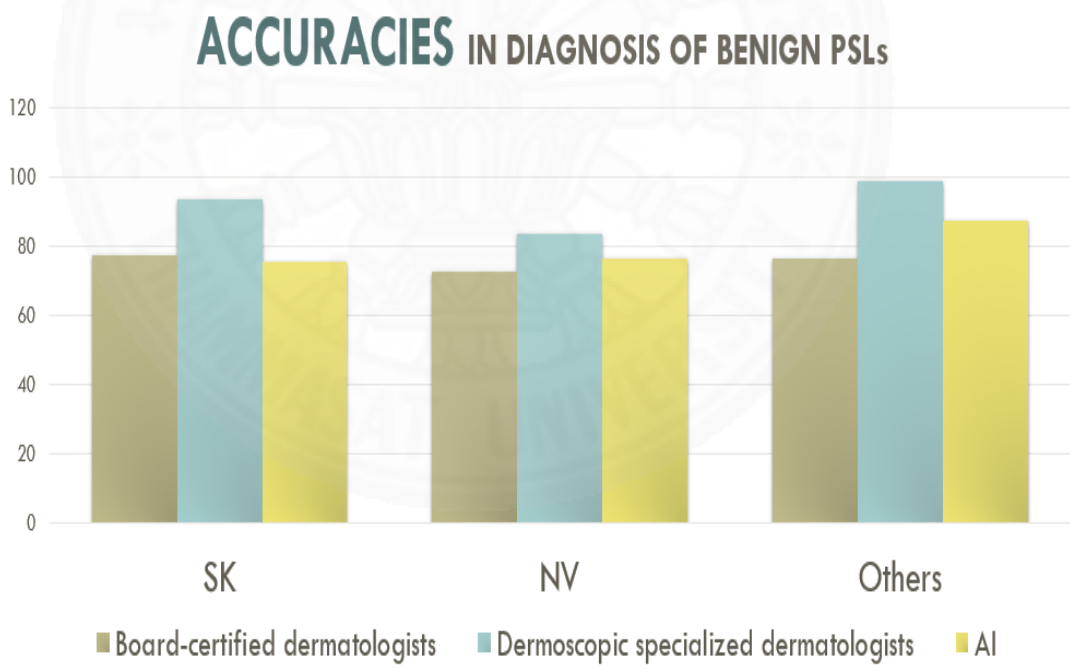


Figure 4.1.3.3 Accuracies in diagnosis of different types of benign pigmented skin lesions compared among three groups

4.1.3.4 Positive predictive values (PPV)

PPVs in diagnosis of benign pigmented lesions were highest in dermoscopic specialized dermatologists. (see *Figure 4.1.3.4*)

In seborrheic keratosis diagnosis, PPVs of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 56.0%, 58.6%, and 90.9% respectively.

For nevus diagnosis, PPVs of AI system, Board- certified dermatologists, and dermoscopic specialized dermatologists were 61.8%, 64.3%, and 84.1% respectively.

For other lesions diagnosis, PPVs of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 15.4%, 12.8%, and 80.3% respectively.

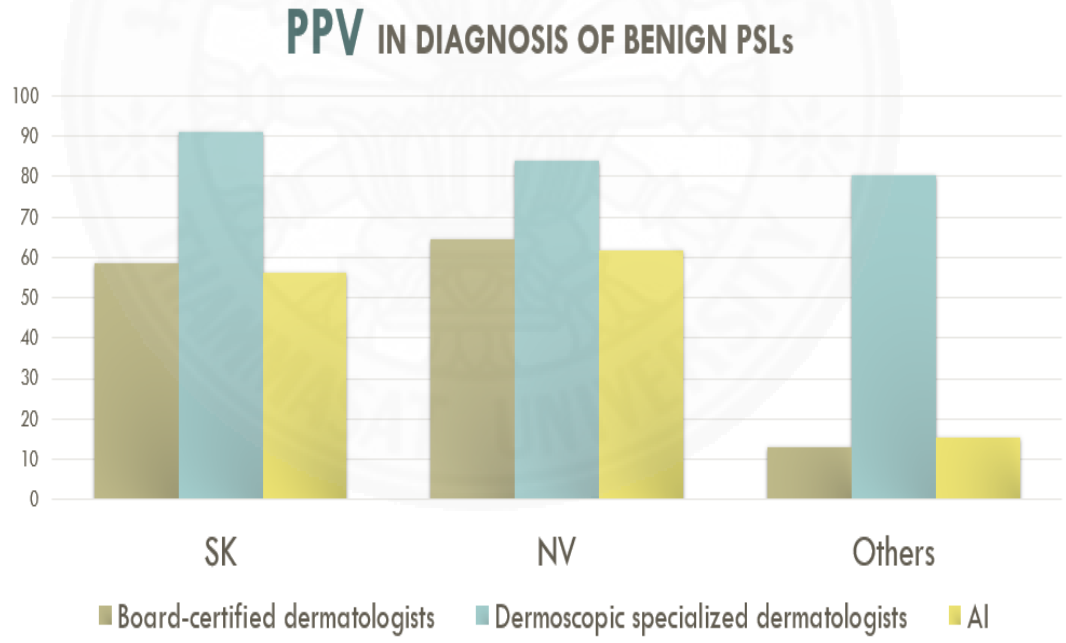


Figure 4.1.3.4 Positive predictive values (PPV) in diagnosis of different types of benign pigmented skin lesions compared among three groups

4.1.3.5 Negative predictive values (NPV)

NPVs in benign pigmented lesions diagnosis among three groups were not different. (see *Figure 4.1.3.5*)

In seborrheic keratosis diagnosis, NPVs of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 78.3%, 86.1%, and 94.3% respectively.

For nevus diagnosis, NPVs of AI system, Board- certified dermatologists, and dermoscopic specialized dermatologists were 85.5%, 74.2%, and 84.4% respectively.

For other lesions diagnosis, NPVs of AI system, Board-certified dermatologists, and dermoscopic specialized dermatologists were 98.3%, 99.8%, and 99.7% respectively.

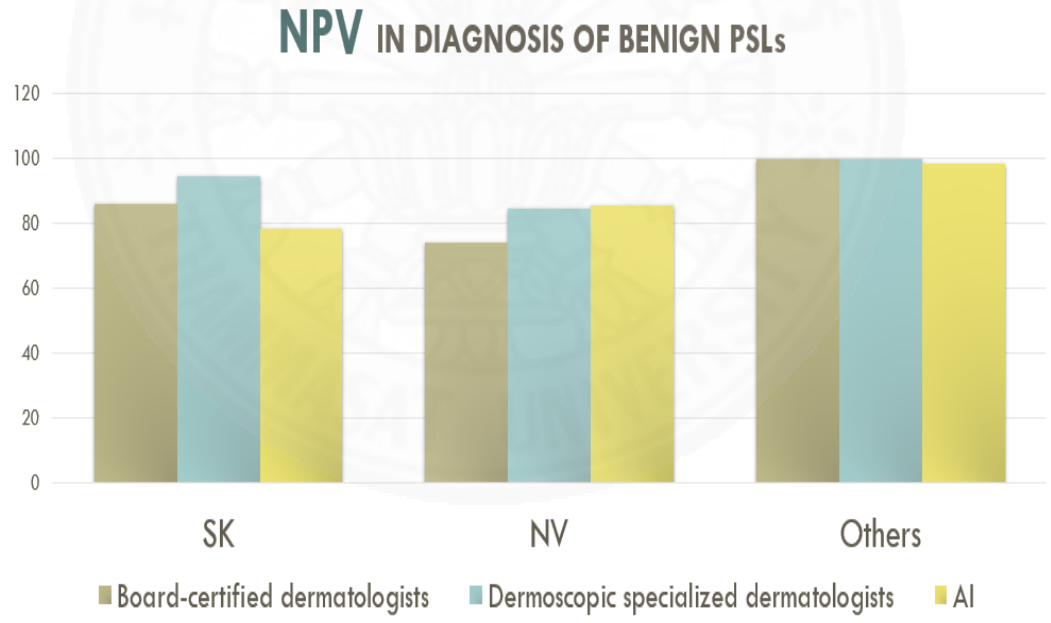


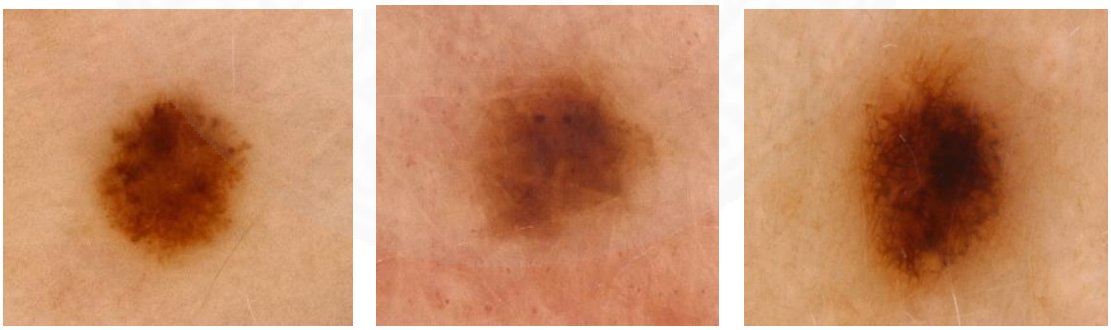
Figure 4.1.3.5 Negative predictive values (NPV) in diagnosis of different types of benign pigmented skin lesions compared among three groups

4.2 Discussion

From previous study, artificial intelligence (AI) system showed outperformances in melanoma, nevus, and seborrheic keratosis diagnosis up to 80-90% of area under ROC curve. All dermoscopic images used to train and assess effectiveness of all classifiers in that work were based on the ISIC Challenge 2017 data.

This is the first study to demonstrate clinical validation test of artificial intelligence (AI) assisted in skin cancer screening system in Thailand using *clinical* dermoscopic images and compared with Board-certified dermatologists vs experienced dermoscopic specialized dermatologists.

Our validation test was very challenging that even Board- certified dermatologists performed with low sensitivity (22.6%) in melanoma diagnosis. In test dataset, 31 correctly dermoscopic images of melanoma were included 18 malignant melanomas and 13 melanomas in situ. Normally, to distinguish among three lesions which are melanoma, melanoma in situ, and nevus, are very difficult task for even the expertise due to similarity in morphologies, colors, and textures as shown in *Figure 4.2a and 4.2b*



a) *b)* *c)*

Figure 4.2.1a, b, c Clinical dermoscopic images in test dataset of
a) melanoma
b) melanoma in situ
c) nevus

From confusion matrix of AI system performance, AI mostly misdiagnosed of melanoma into nevus from 9 out of 31 images. And 4 out of 9 false negatives which

account for almost 50%, are melanoma in situ condition. This might also interpret that false negatives in melanoma are majorly due to similarity among melanoma, melanoma in situ, and nevus. (see *Figure 4.2.2*)

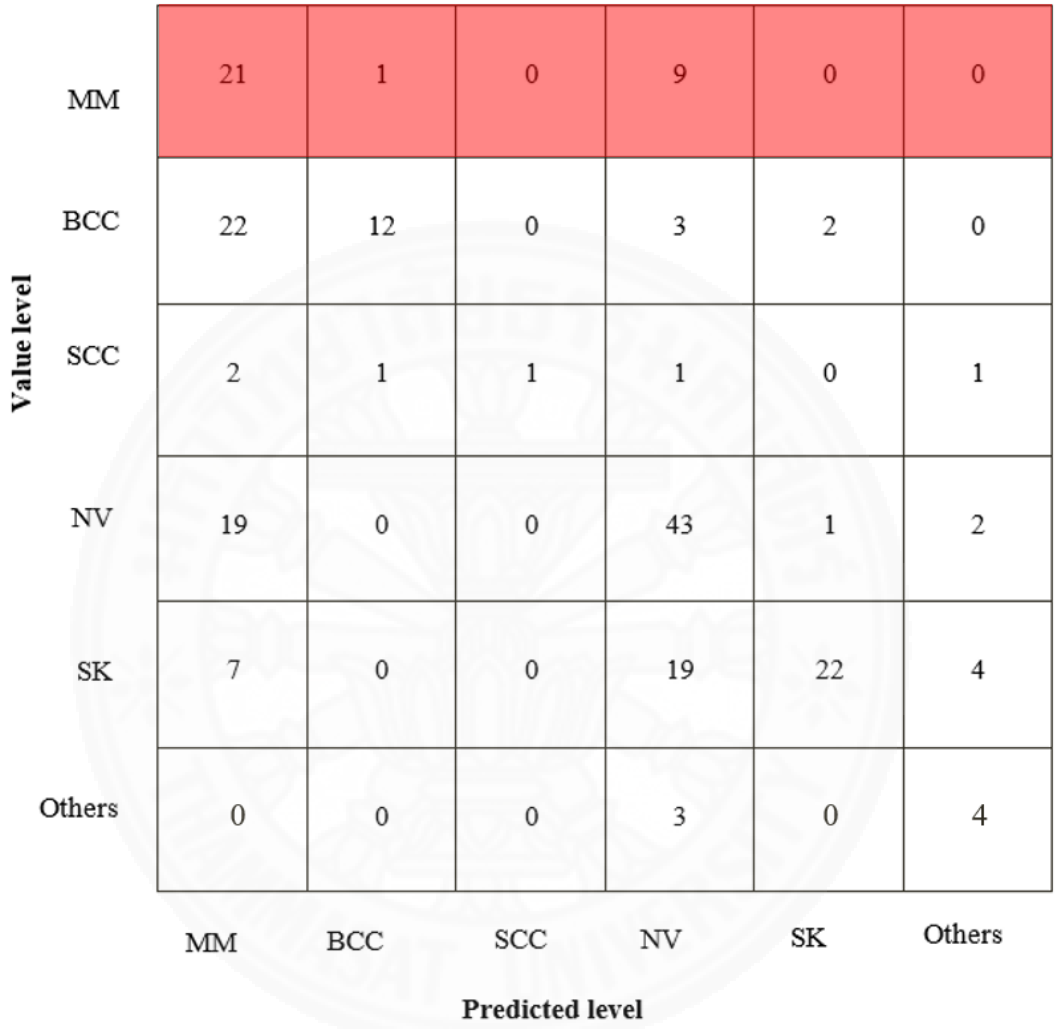


Figure 4.2.2a Confusion matrix of AI system performance: melanoma classification

However, AI system had higher sensitivity (67.7%) in melanoma diagnosis compared to Board-certified dermatologists (22.6%) and almost the same level as dermoscopic specialized dermatologists (69.9%).

For other types of skin cancers diagnosis which either basal cell carcinoma or squamous cell carcinoma, AI system's diagnostic performances were still disappointing. AI had lower sensitivities compared to Board-certified dermatologists and experienced dermoscopic specialized dermatologists (30.8% vs 42.7% vs 66.7% in

BCC diagnosis, and 16.7% vs 16.7% vs 72.2% in SCC diagnosis). This might be the reflection from scarcity of dermoscopic images of BCC and SCC used to train AI system. (see *Table 4.2*)

Table 4.2 Sources of trained dataset

TRAINED DATASET	MM	SK	NV	BCC	SCC
ISIC 2017	374	254	1372	-	-
Smitivej hospital	25	-	-	22	3
Textbooks	217	40	-	47	8
Journal articles	-	-	-	102	18
Total	616	346	1372	171	29

Interestingly, most of false negatives for BCC and SCC classification were melanomas which were still malignant. This showed that AI performances in differentiating malignancy and benign were acceptable.

For BCC classification, if we re-classify into cancer and non-cancer categories, sensitivity in diagnosis increases significantly up to 81.18%. (see *Figure 4.2.2b*)

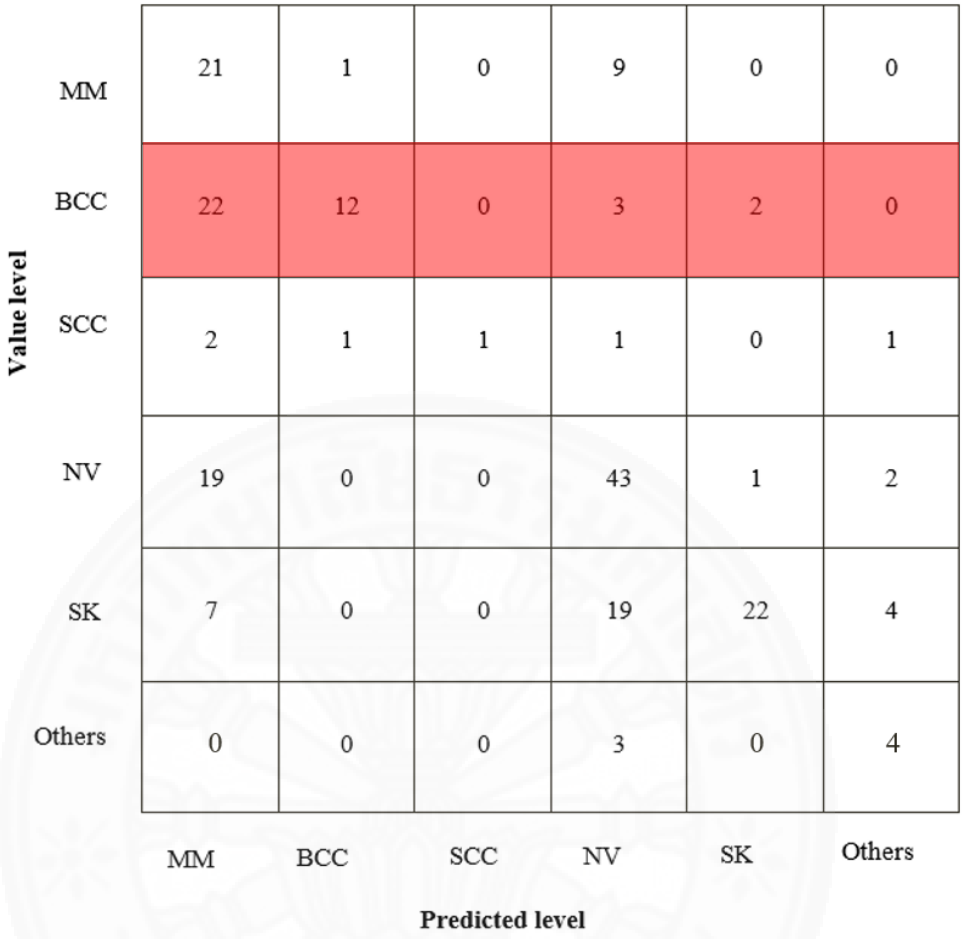


Figure 4.2.2b Confusion matrix of AI system performance: BCC classification

For SCC classification, most of false negatives were melanoma. If we re-classify into cancer and non-cancer categories, sensitivity in diagnosis increases up to 66.67%. (see *Figure 4.2.2c*)

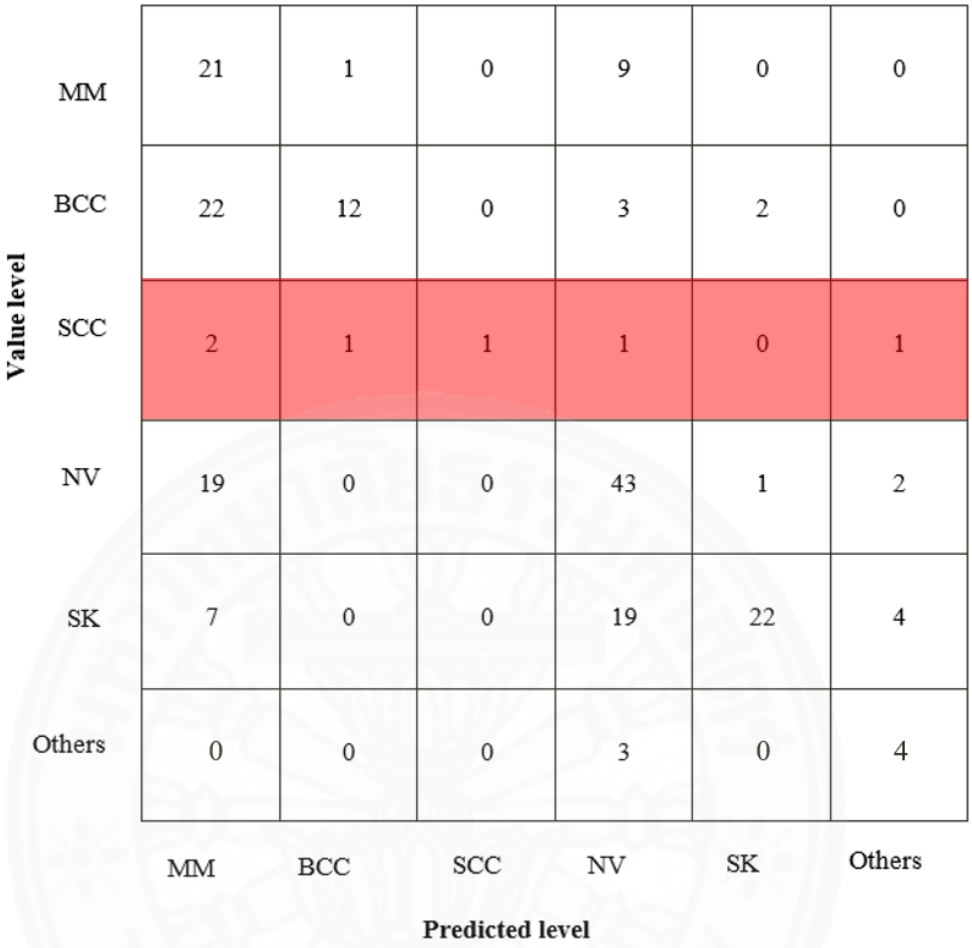


Figure 4.2.2c Confusion matrix of AI system performance: SCC classification

In benign pigmented skin lesions diagnosis, AI system had highest sensitivity in nevus category, but lowest in seborrheic keratosis and other lesions categories. From the results, we might conclude that the more images used to train AI, the better diagnostic performances.

Although diagnostic performance of our AI system in diagnosis of skin cancers was not achieved with high diagnostic performances as the results in our previous experiment using ISIC 2017 images as validation test, this was the first start to develop AI system to be applied in real clinical setting.

Scarcity of dermoscopic images used to train AI algorithm was the major limitation for improving diagnostic accuracy.

CHAPTER 5
CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Our artificial intelligence system using deep learning computer vision algorithm achieved performance in diagnosis of melanomas with similar level as Board-certified dermatologists. However, in other skin cancers classification which were basal cell carcinomas and squamous cell carcinomas, AI still needed to be trained more to improve diagnostic accuracy.

5.2 Recommendations

5.2.1 AI system still need further trainings to improve its outcomes before applying in clinical settings especially in melanoma in situ, basal cell carcinoma and squamous cell carcinoma categories.

5.2.2 The more images you train AI, the better outcome you can get in the future. Other sources of images may gather from other medical centers or open public to physicians.

5.2.3 Add on algorithm such as ABCD rule to AI system to be trained to reach better performances.

5.2.4 In practice, classification of cancer versus non-cancer is the most essential point. Too many categories in classification may not helpful in case that AI system still has learning limitation.

5.2.5 Larger sample size and prospective study may be necessary for the further studies.

REFERENCES

1. Oakley A. Pigmented skin lesions New Zealand2015 [Available from: https://www.dermnetnz.org/topics/pigmented-skin-lesions.

2. S. B. The assessment, history taking and differential diagnosis of pigmented skin lesions. Dermatological nursing. 2015;14(4):18-22.

3. Garcia R, Korotkov K, Korotkov K, Garcia R. Computerized analysis of pigmented skin lesions: A review.

4. Thomas L, Puig S. Dermoscopy, Digital Dermoscopy and Other Diagnostic Tools in the Early Detection of Melanoma and Follow-up of High-risk Skin Cancer Patients. Acta Dermato-Venereologica. 2017;97:14-21.

5. Bolognia J, Jorizzo J, Schaffer J. Dermatology, third edition. London: Elsevier; 2012.

6. Soyer P, Argenziano G, Ruocco V, Chimenti S. Dermoscopy of Pigmented Skin Lesions2001. 483-98 p.

7. Goldsmith L, Katz S, Gilchrest B, Paller A, Leffell D. Fitzpatrick's Dermatology in general medicine, 8th edition. United States of America: The McGraw-Hill Companies, Inc. ; 2012.

8. Ngan V. Spitz naevus 2003 [Available from: https://www.dermnetnz.org/topics/spitz-naevus/.

9. Yoradjian A, Enokihara MM, Paschoal FM. Spitz nevus and Reed nevus. Anais brasileiros de dermatologia. 2012;87(3):349-57; quiz 58-9.

10. Gibson L. Melanoma: Mayo clinic; 2017 [Available from: https://www.mayoclinic.org/diseases-conditions/melanoma/symptoms-causes/syc-20374884.

11. Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Bastholt L, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline - Update 2016. Eur J Cancer. 2016;63:201-17.

12. Society AC. Cancer facts & figures 2016 Atlanta2016 [Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2016.html.

13. Valachovic E, Zurbenko I. Multivariate analysis of spatial–temporal scales in melanoma prevalence. Cancer Causes & Control. 2017;28(7):733-43.

14. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

15. Bhattacharya A, Young A, Wong A, Stalling S, Wei M, Hadley D. Precision Diagnosis Of Melanoma And Other Skin Lesions From Digital Images. AMIA Joint Summits on Translational Science proceedings AMIA Joint Summits on Translational Science. 2017;2017:220-6.

16. Davey RJ, van der Westhuizen A, Bowden NA. Metastatic melanoma treatment: Combining old and new therapies. Crit Rev Oncol Hematol. 2016;98:242-53.

17. Bichakjian CK, Halpern AC, Johnson TM, Foote Hood A, Grichnik JM, Swetter SM, et al. Guidelines of care for the management of primary cutaneous melanoma. American Academy of Dermatology. Journal of the American Academy of Dermatology. 2011;65(5):1032-47

18. Harries M, Malvehy J, Lebbe C, Heron L, Amelio J, Szabo Z, et al. Review: Treatment patterns of advanced malignant melanoma (stage III–IV) – A review of current standards in Europe. European Journal of Cancer. 2016;60:179-89.

19. Abbasi NR, Shaw HM, Rigel DS, Polsky D, Friedman RJ, Kopf AW, et al. Early diagnosis of cutaneous melanoma: Revisiting the ABCD criteria. JAMA, The Journal of the American Medical Association. 2004(22):2771.

20. Mackie RM, Doherty VR. Seven-point checklist for melanoma. Clinical & Experimental Dermatology. 1991;16(2):151.

21. Gordon R. Skin Cancer: An Overview of Epidemiology and Risk Factors. Seminars in Oncology Nursing. 2013;29(3):160-9.

22. Morton, Mackie. Clinical accuracy of the diagnosis of cutaneous malignant melanoma. British Journal of Dermatology. 1998;138(2):283.

23. Lindelöf B, Hedblad MA. Accuracy in the Clinical Diagnosis and Pattern of Malignant Melanoma at a Dermatological Clinic. The Journal of Dermatology. 1994;21(7):461.

24. Grin CM, Kopf AW, Welkovich B, Bart RS, Levenstein MJ. Accuracy in the clinical diagnosis of malignant melanoma. Arch Dermatol. 1990;126(6):763-6.

25. Gachon J, Beaulieu P, Sei JF, Gouvernet J, Claudel JP, Lemaitre M, et al. First prospective study of the recognition process of melanoma in dermatological practice. Arch Dermatol. 2005;141(4):434-8.

26. Masood A, Al-Jumaily AA. Computer aided diagnostic support system for skin cancer: a review of techniques and algorithms. Int J Biomed Imaging. 2013;2013:323268.

27. Modern non-invasive diagnostic techniques in the detection of early cutaneous melanoma. Journal of Dermatological Case Reports; 2014. p. 1-8.

28. Argenziano G, Fabbrocini G, Carli P, De Giorgi V, Sammarco E, Delfino M. Epiluminescence Microscopy for the Diagnosis of Doubtful Melanocytic Skin Lesions: Comparison of the ABCD Rule of Dermatoscopy and a New 7-Point Checklist Based on Pattern Analysis. Archives of Dermatology. 1998;134(12):1563.

29. Binder M. Epiluminescence microscopy of small pigmented skin lesions: Short-term formal training improves the diagnostic performance of dermatologists. 1997:197.

30. Pehamberger H, Binder M, Steiner A, Wolff K. In Vivo Epiluminescence Microscopy: Improvement of Early Diagnosis of Melanoma. Journal of Investigative Dermatology. 1993;100(3):356S-62S.

31. Carli P, De Giorgi V, Crocetti E, Mannone F, Massi D, Chiarugi A, et al. Improvement of malignant/benign ratio in excised melanocytic lesions in the 'dermoscopy era': a retrospective study 1997-2001. The British journal of dermatology. 2004;150(4):687-92.

32. Carli P, de Giorgi V, Chiarugi A, Nardini P, Weinstock MA, Crocetti E, et al. Report: Addition of dermoscopy to conventional naked-eye examination in melanoma screening: a randomized study. Journal of the American Academy of Dermatology. 2004;50:683-9.

33. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. Lancet Oncology. 2002(3):159.

34. Hossam D, Sadek A, Saied N. Dermoscopy: A Literature Review. Egyptian Dermatology Online Journal. 2015;11(1):1-32.

35. Scope A, Benvenuto-Andrade C, Agero ALC, Marghoob AA. Nonmelanocytic Lesions Defying the Two-Step Dermoscopy Algorithm. Dermatologic Surgery. 2006;32(11):1398.

36. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: a new dermoscopic algorithm for the diagnosis of malignant melanoma. European journal of dermatology : EJD. 1999;9(4):303-8.

37. Soyer HP, Argenziano G, Zalaudek I, Corona R, Sera F, Talamini R, et al. Three-point checklist of dermoscopy. A new screening method for early detection of melanoma. Dermatology (Basel, Switzerland). 2004;208(1):27-31.

38. Pehamberger H, Steiner A, Wolff K. In vivo epiluminescence microscopy of pigmented skin lesions. I. Pattern analysis of pigmented skin lesions. Journal of the American Academy of Dermatology. 1987;17:571-83.

39. Nachbar F, Stolz W, Merkle T, Cognetta AB, Vogt T, Landthaler M, et al. The ABCD rule of dermatoscopy. High prospective value in the diagnosis of doubtful melanocytic skin lesions. Journal of the American Academy of Dermatology. 1994;30(4):551-9.

40. Rajpara SM, Botello AP, Townend J, Ormerod AD. Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma. The British journal of dermatology. 2009;161(3):591-604.

41. Kittler H, Pehamberger H, Wolff K, Binder M. Review: Diagnostic accuracy of dermoscopy. Lancet Oncology. 2002;3:159-65.

42. Piccolo D, Ferrari A, Peris K, Daidone R, Ruggeri B, Chimenti S. Dermoscopic diagnosis by a trained clinician vs. a clinician with minimal dermoscopy training vs. computer-aided diagnosis of 341 pigmented skin lesions: a comparative study. British Journal of Dermatology. 2002;147(3):481-6.

43. Chang W-Y, Huang A, Yang C-Y, Lee C-H, Chen Y-C, Wu T-Y, et al. Computer-Aided Diagnosis of Skin Lesions Using Conventional Digital Photography: A Reliability and Feasibility Study. PLoS ONE. 2013(11).

44. Smoller BR. Histologic criteria for diagnosing primary cutaneous malignant melanoma. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2006;19 Suppl 2:S34-40.

45. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(36):6199-206.

46. Ackerman AB. Discordance among expert pathologists in diagnosis of melanocytic neoplasms. Human pathology. 1996;27(11):1115-6.

47. Farmer ER, Gonin R, Hanna MP. Discordance in the histopathologic diagnosis of melanoma and melanocytic nevi between expert pathologists. Human pathology. 1996;27(6):528-31.

48. Prakashini K, Babu S, Rajgopal KV, Kokila KR. Role of Computer Aided Diagnosis (CAD) in the detection of pulmonary nodules on 64 row multi detector computed tomography. Lung India. 2016;33(4):391-7.

49. Jiang L, Uitert RV, Jianhua Y, Petrick N, Franaszek M, Huang A, et al. Wavelet method for CT colonography computer-aided polyp detection. Medical Physics. 2008;35(8):3527.

50. Houssami N, Given-Wilson R, Ciatto S. Early detection of breast cancer: Overview of the evidence on computer-aided detection in mammography screening. Journal of Medical Imaging & Radiation Oncology. 2009;53(2):171-6.

51. Fenton JJ, Taplin SH, Carney PA, Abraham L, Sickles EA, D'Orsi C, et al. Influence of computer-aided detection on performance of screening mammography. The New England Journal of Medicine. 2007(14):1399.

52. Fujita H, Katafuchi T, Uehara T, Nishimura T. Application of Artificial Neural Network to Computer-Aided Diagnosis of Coronary Artery Disease in Myocardial SPECT Bull's-eye Images. Journal of Nuclear Medicine. 1992;33(2):272.

53. Lindahl, Palmer, Edenbrandt, Lindahl D. Myocardial SPET: artificial neural networks describe extent and severity of perfusion defects. Clinical Physiology. 1999;19(6):497-503.

54. Fernandez-Penas P. Diagnostic and neural analysis of skin cancer (DANAOS). A multicentre study for collection and computer-aided analysis of data from pigmented skin lesions using digital dermoscopy. British Journal of Dermatology. 2003;149:801-9.

55. Schmid-Saugeona P, Guillodb J, Thirana J-P. Towards a computer-aided diagnosis system for pigmented skin lesions. Computerized Medical Imaging and Graphics. 2003;27:65-78.

56. Zortea M, Schopf TR, Thon K, Geilhufe M, Hindberg K, Kirchesch H, et al. Performance of a dermoscopy-based computer vision system for the diagnosis of pigmented skin lesions compared with visual evaluation by experienced dermatologists. Artificial Intelligence in Medicine. 2014;60(1):13-26.

57. Hall PN, Claridge E, Smith JDM. Computer screening for early detection of melanoma -- is there a future? British Journal of Dermatology. 1995;132(3):325.

58. Cascinelli N, Ferrario M, Tonelli T, Leo E. A possible new tool for clinical diagnosis of melanoma: The computer. Journal of the American Academy of Dermatology. 1987;16(Part 1):361-7.

59. Cristofolini M, Bauer P, Boi S, Cristofolini P, Micciolo R, Sicher MC. Diagnosis of cutaneous melanoma: accuracy of a computerized image analysis system (Skin View). Skin Research & Technology. 1997;3(1):23.

60. Ferri M. Computer-aided diagnosis of melanocytic lesions.

61. Rubegni P. Automated diagnosis of pigmented skin lesions.

62. Premaladha J, Ravichandran KS. Novel Approaches for Diagnosing Melanoma Skin Lesions Through Supervised and Deep Learning Algorithms. Journal of Medical Systems. 2016;40(4):96.

63. Liu Z, Sun J, Smith L, Smith M, Warr R, Liu Z, et al. Distribution quantification on dermoscopy images for computer-assisted diagnosis of cutaneous melanomas. Medical & Biological Engineering & Computing. 2012;50(5):503-13.

64. Mokhtari M, Rezaeian M, Gharibzadeh S, Malekian V. Computer aided measurement of melanoma depth of invasion in microscopic images. Micron. 2014;61:40-8.

65. Jaworek-Korjakowska J, Kłeczek P. Automatic Classification of Specific Melanocytic Lesions Using Artificial Intelligence. BioMed Research International. 2016;2016:1-17.

66. Li L, Clark A, Wang JZ, editors. A Computer-Aided Diagnostic Tool for Melanoma. 2014 International Conference on Computational Science and Computational Intelligence; 2014 10-13 March 2014.

67. Kruk M, Świderski B, Osowski S, Kurek J, Słowińska M, Walecka I. Melanoma recognition using extended set of descriptors and classifiers. EURASIP Journal on Image & Video Processing. 2015;2015(1):1.

68. Patient acceptance and diagnostic utility of automated digital image analysis of pigmented skin lesions. Journal of the European Academy of Dermatology and Venereology. 2012(3):368.

69. Ercal F, Chawla A, Stoecker WV, Lee HC, Moss RH. Neural network diagnosis of malignant melanoma from color images. IEEE transactions on bio-medical engineering. 1994;41(9):837-45.

70. Elbaum M, Kopf AW, Rabinovitz HS, Langley RGB, Kamino H, Mihm JMC, et al. Reports: Automatic differentiation of melanoma from melanocytic nevi with multispectral digital dermoscopy: A feasibility study. Journal of the American Academy of Dermatology. 2001;44(Part 1):207-18.

71. Seidenari S, Pellacani G, Pepe P. Digital videomicroscopy improves diagnostic accuracy for melanoma. Journal of the American Academy of Dermatology. 1998;39(2 Pt 1):175-81.

72. Rubegni P. Digital dermoscopy analysis and artificial neural network for the differentiation of clinically atypical pigmented skin lesions: A retrospective study.

73. Monga K. Mining Medical Records: A Case for Artificial Intelligence in Health Systems. Journal of AHIMA. 2017;88(10):54-6.

74. Moor J. The Dartmouth College Artificial Intelligence Conference: The Next Fifty Years. 2006:87.

75. LeCun Y, Bengio Y, Hinton G. Deep learning. Nature. 2015;521:436.

76. Andrew J, Anant M. Deep learning for digital pathology image analysis: A comprehensive tutorial with selected use cases. Journal of Pathology Informatics, Vol 7, Iss 1, Pp 29-29 (2016). 2016(1):29.

77. Nasr-Esfahani E, Samavi S, Karimi N, Soroushmehr SM, Jafari MH, Ward K, et al. Melanoma detection by analysis of clinical images using convolutional neural network. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference. 2016;2016:1373-6.

78. Marchetti MA, Codella NCF, Dusza SW, Gutman DA, Helba B, Kalloo A, et al. Results of the 2016 International Skin Imaging Collaboration International Symposium on Biomedical Imaging challenge: Comparison of the accuracy of

computer algorithms to dermatologists for the diagnosis of melanoma from dermoscopic images. Journal of the American Academy of Dermatology. 2017.

79. Kirkwood J. The Human Element in ARTIFICIAL INTELLIGENCE: As the promise of machine learning grows, so does the need for clinical expertise and collaboration. Clinical Laboratory News. 2017;43(11):12-6.

80. Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;546(7639).

81. Huang G, Liu Z, Maarten L, Weinberger K. Densely Connected Convolutional Networks. 2017:2261.

82. An Ensemble of Fine-Tuned Convolutional Neural Networks for Medical Image Classification. IEEE Journal of Biomedical and Health Informatics, Biomedical and Health Informatics, IEEE Journal of, IEEE J Biomed Health Inform. 2017(1):31.

83. Deep Residual Learning for Image Recognition. IEEE; 2016. p. 770.

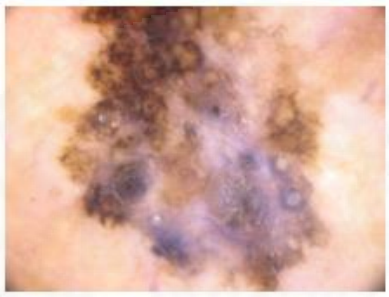
84. Sawankachirdwilai P, Pusowan A, Kethirun P, Sombune P, Tantibundhit C. Automated melanoma recognition in dermoscopic images: comparison of ResNets, DenseNets, Their 3-Binary counterparts, and GANs Integration to improve classification results. IEEE transactions on bio-medical engineering. 2018.

85. Liberman M. Biomedical nerdview 2014 [Available from: http://languagelog.l-dc.upenn.edu/nll/?p=14835.

APPENDICES

APPENDIX A
CASE RECORD FORM

Collecting dermoscopic images of pigmented skin lesions from medical records in Samitivej Sukhumvit hospital.

1. 

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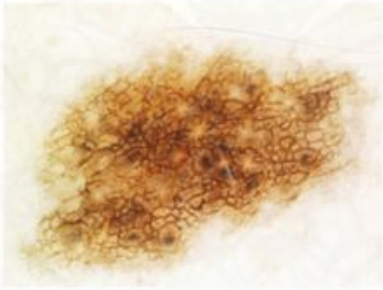
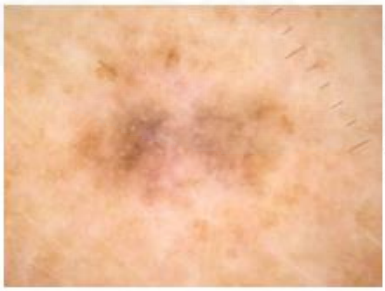
อายุ.....
ตำแหน่งที่ถ่าย.....
ผลการวินิจฉัย.....
ผลตรวจชิ้นเนื้อ pathology.....

2. 

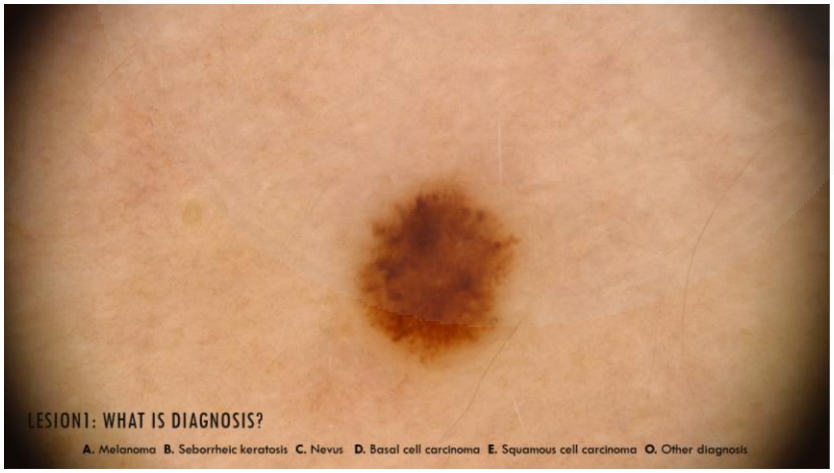
เพศ.....
อายุ.....
ตำแหน่งที่ถ่าย.....
ผลการวินิจฉัย.....
ผลตรวจชิ้นเนื้อ pathology.....

3. 

เพศ.....
อายุ.....
ตำแหน่งที่ถ่าย.....
ผลการวินิจฉัย.....
ผลตรวจชิ้นเนื้อ pathology.....

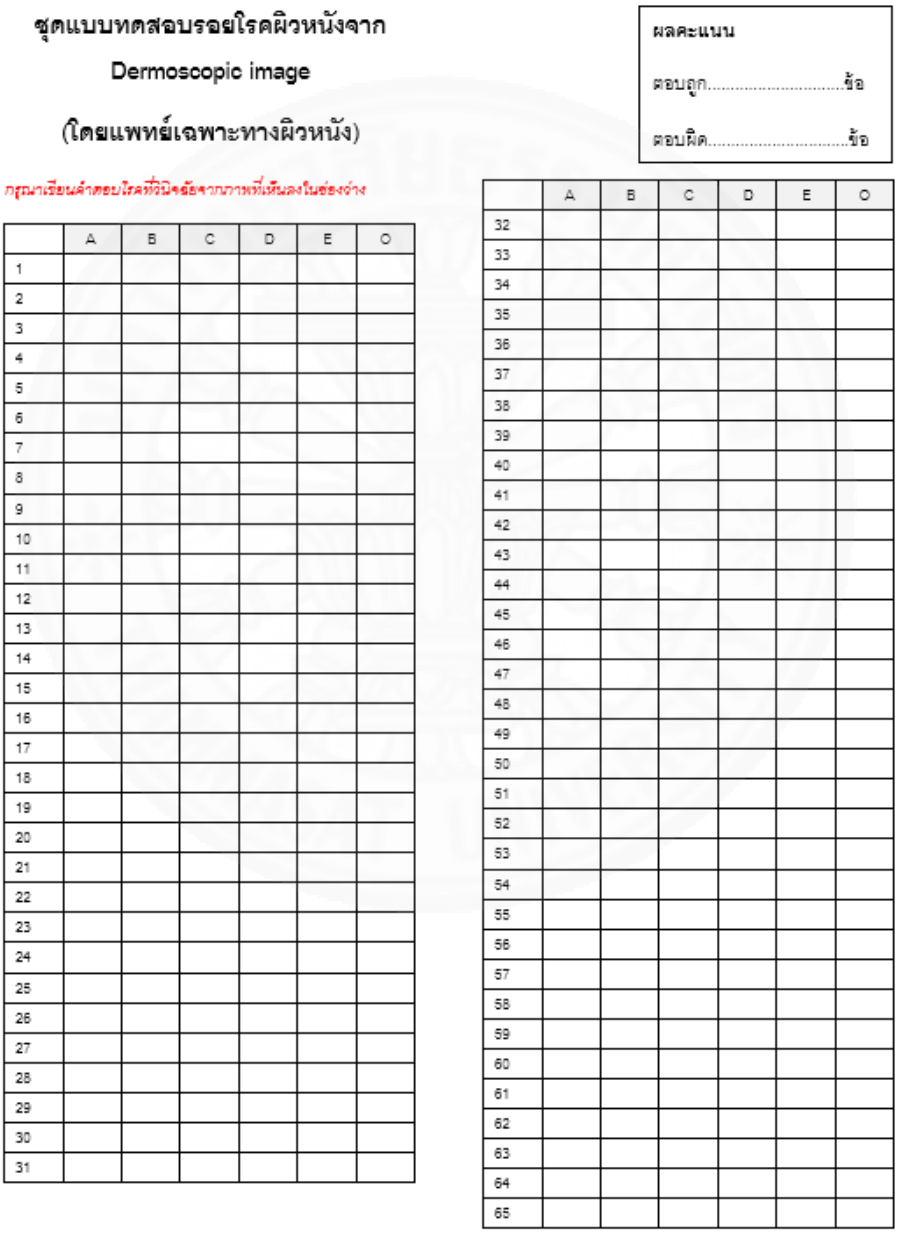
APPENDIX B
TEST DATASET FOR DERMATOLOGISTS

Test dataset contains 200 dermoscopic images of pigmented skin lesions. Each image provides multiple choices including; A. Melanoma, B. Seborrheic keratosis, C. Nevus, D. Basal cell carcinoma, E. Squamous cell carcinoma.



APPENDIX C
ANSWER SHEET

Answer sheet of test dataset for dermatologists. This test is allowed to choose only one correct answer of each image.



ชุดแบบทดสอบรอยโรคผิวหนังจาก

Dermoscopic image

(โดยแพทย์เฉพาะทางผิวหนัง)

ผลคะแนน

ตอบถูก.....ข้อ

ตอบผิด.....ข้อ

กรุณาเขียนคำตอบโรคที่วินิจฉัยจากภาพที่เห็นลงในช่องว่าง

	A	B	C	D	E	O
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	A	B	C	D	E	O
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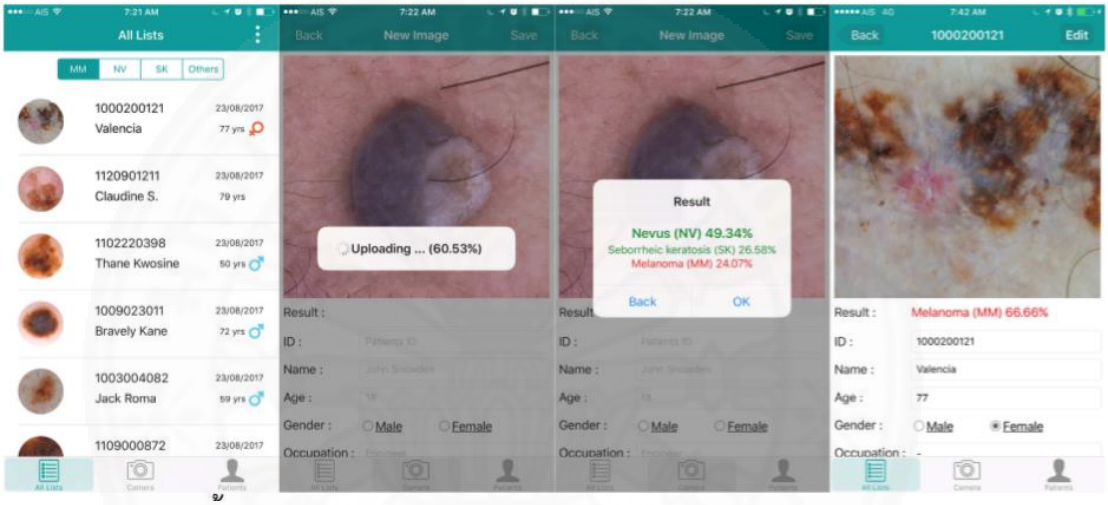
APPENDIX D

SMARTPHONE APPLICATION OF AI ASSISTED IN SKIN CANCERS SCREENING SYSTEM

Smartphone application called “Cutis.AI”



BIOGRAPHY

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Publications	N/A
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