Benefits and Risks with Digital Dermoscopy and Teledermoscopy

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Cover image: Smartphone with compatible dermoscope attached as used during teledermoscopy. The dermoscopic image on the screen is a melanoma.
Photo: Johan Dahlén Gyllencreutz

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“It was solid
Yet Everchanging
It was different
Yet the same”

From Therein by Dark Tranquillity,

Abstract

The increasing incidence of malignant melanoma and non-melanoma skin cancer (NMSC) makes it necessary to optimise the management of patients with suspicious skin lesions, from triaging, to establishing a diagnosis and planning treatment. The purpose of this thesis is to investigate the use of teledermoscopy (TDS) as a way of achieving such an optimisation, as well as to study safety aspects of digital dermoscopy and teledermoscopy while pointing out risks and pitfalls so that they can be avoided.

In study I, smartphone TDS was compared with traditional paper referrals. The outcome of 772 patients referred by TDS from 20 primary health care (PHC) centres to two dermatology departments was compared to that of 746 patients referred without images. TDS provided faster management of patients with skin cancer and more accurate prioritisation. In study II, 80 TDS referrals and 77 paper referrals were evaluated by six dermatologists, resulting in moderate interobserver concordance. The diagnostic agreement with TDS was higher for several diagnoses. It also proved easier to plan for surgery at the first visit and to resend referrals with clearly benign lesions. However, a few referrals with malignant lesions were incorrectly resent. In study III, two dermatologists compared the image quality of 172 dermoscopic images acquired in PHC with images of the same tumours obtained at the department of dermatology. The PHC images were of slightly lower quality but the difference was not statistically significant. No difference was found in the ability to correctly diagnose the lesions. In study IV, dermoscopic images of skin lesions, obtained before and after the use of a sunless tanning product containing dihydroxyacetone (DHA), were compared. For facial lesions, there were significantly more equivocal lesions after the use of DHA. A follicular pigmentation was often found, somewhat mimicking that of lentigo maligna.

In conclusion, TDS can result in safer, more efficient management of patients with skin lesions of concern, earlier treatment of patients with malignant lesions and fewer unnecessary visits to a dermatologist. TDS images obtained in PHC are of similar quality to those obtained by trained dermatologists. When triaging TDS referrals, dermatologists should avoid resending referrals for clinically atypical melanocytic lesions and take into consideration the use of pigment-altering substances such as DHA.

Keywords: Melanoma, non-melanoma skin cancer, dermoscopy, teledermoscopy, teledermatology, e-health

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Sammanfattning på svenska

Hudcancer (innefattande främst malignt melanom, skivepitelcancer och basalcellscancer) tillhör de snabbast ökande cancerformerna i Sverige och många andra länder. Detta, i kombination med att många i befolkningen söker vård för vad som visar sig vara godartade hudförändringar, bidrar till att antalet hudtumörremisser ökar kraftigt. De utgör ofta över 50 % av remisserna från vårdcentraler till hudkliniker. För att patienter med hudcancer ska komma till bedömning och behandling tillräckligt snabbt behöver man på ett optimalt sätt organisera varje del av vården, från remittering till ställande av diagnos och planering av behandling. I Sverige söker patienter med hudtumörer oftast först i primärvården. Vid misstanke om hudcancer remitteras patienterna sedan till hudkliniker för bedömning och vid behov behandling. Riktlinjer fastställer hur länge en enskild patient kan få vänta, från att en remiss skickats till besöket på en hudklinik. Dessa riktlinjer utgår från vilken diagnos som misstänks när remissen bedöms. Det innebär att patienter med misstanke om farliga cancerformer som malignt melanom ska bokas snabbast medan de med misstanke om mindre allvarliga tumörformer kan få vänta längre. Vidare behöver de fall där man säkert kan fastställa att tumören är godartad inte alls bedömas på hudklinik. Nuvarande system med pappersremisser, oftast utan bilder, gör det dock svårt att på ett säkert sätt skilja grupperna åt. I de fall där en operation behövs kan det också var svårt att göra detta vid första besöket, då man oftast inte har kännedom om behovet av en operation på förhand. Detta gör att det kan behövas flera besök innan behandling är genomförd.

På hudkliniker bedöms hudtumörer rutinmässigt med dermatoskopi, en metod som genom förstoring och belysning ger möjlighet att visualisera strukturer i överhud och läderhud. Detta ökar möjligheterna att ställa rätt diagnos vid bedömning av hudtumörer och på så sätt både minska risken för att missa hudcancer och för att godartade tumörer behandlas i onödan. När man använder digitala bilder tagna med ett dermatoskop kallas det digital dermatoskopi och när dessa bilder skickas elektroniskt, t.ex. i en remiss, kallas detta teledermatoskopi (TDS). Syftet med denna avhandling är att studera hur användning av TDS påverkar handläggning av patienter med hudcancer, från prioritering till bedömning och behandling. Säkerhetsaspekter av digital dermatoskopi och TDS studeras också.

I studie I jämfördes utfallet för 772 patienter remitterade med TDS-remisser skickade med hjälp av en smartmobil, med 746 patienter remitterade med vanlig pappersremiss. Med TDS blev prioriteringen av remisserna bättre vilket innebär att det var lättare att korrekt klassa varje fall enligt de riktlinjer som finns för elakartade och godartade

tumörer. Tid till bedömning och behandling av malignt melanom och övrig hudcancer blev också kortare.

I studie II gjordes ett slumpmässigt urval av 80 TDS-remisser och 77 pappersremisser från studie I, med en jämn fördelning mellan de prioriteringsgrupperna som finns för hudtumörer. Remisserna bedömdes av sex hudläkare utan tidigare kännedom om fallen. För malignt melanom och flera andra tumörsorter gjorde TDS det möjligt att säkrare ställa diagnos medan det för vanligare tumörsorter inte var en lika tydlig skillnad mellan TDS och pappersremiss. Samstämmigheten i bedömningen var måttligt god med båda remissmetoderna. Det visade sig också möjligt att med TDS boka fler patienter med hudcancer till operation vid första besöket och att man kunde skicka tillbaka fler remisser för godartade tumörer till vårdcentral. Enstaka fall av hudcancer skickades dock felaktigt tillbaka.

I studie III jämfördes 172 dermatoskopiska remissbilder tagna med smartmobil på vårdcentral, med bilder tagna på samma tumörer men med standardutrustning, på hudklinik. Två hudläkare bedömde bildkvaliteten i bilderna och uttalade sig om diagnos. Ingen statistiskt signifikant skillnad i bildkvalitet kunde ses och möjligheten att ställa korrekt diagnos var lika bra oberoende av var bilderna var tagna.

I studie IV studerades huruvida en produkt av typen ”brun utan sol” innehållande dihydroxiaceton (DHA) påverkar strukturer man ser vid dermatoskopi samt om det kan göra att godartade tumörer ser mer oroande ut. I studien ingick tre bildserier med 38 dermatoskopiska bilder i varje. Bilderna tagna före och efter användning av DHA. Slutsatsen blev att DHA orsakar en tillfällig förändring av de dermatoskopiska strukturerna som ses. Det observerades att hudförändringar i ansiktet, efter användning av DHA, kunde uppvisa strukturer som delvis liknar de man ser vid hudcancer. Detta skulle kunna resultera i onödig provtagning eller behandling.

Avhandlingen visar att man med TDS kan få en snabbare och mer säker handläggning av hudtumörpatienter samt att man kan arbeta mer effektivt och planera vården bättre. TDS med bilder tagna i primärvården kan användas, utan att detta försämrar möjligheten att ställa en preliminär diagnos utifrån bilderna. Åtgärder bör vidtas för att minska risken för att tvetydiga men elakartade tumörer missas. Slutligen bör hänsyn tas för att all information inte är tillgänglig när man bedömer bilder på hudtumörer utan att ha patienten på plats, inklusive användning av pigmentgivande ämnen så som DHA.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Börve A, Dahlén Gyllencreutz J, Terstappen K, Johansson Backman E, Aldenbratt A, Danielsson M, Gillstedt M, Sandberg C, Paoli J.
Smartphone Teledermoscopy Referrals: A Novel Process for Improved Triage of Skin Cancer Patients.
Acta Derm Venereol 2015; 95: 186–190

II. Dahlén Gyllencreutz J, Paoli J, Bjellerup M, Bucharbajeva Z, Gonzalez H, Nielsen K, Sandberg C, Synnerstad I, Terstappen K, Wennberg Larkö AM.
Diagnostic Agreement and Interobserver Concordance with Teledermoscopy Referrals.
J Eur Acad Dermatol Venereol. 2017; 31: 898-903

III. Dahlén Gyllencreutz J, Johansson Backman E, Terstappen K, Paoli J.
Teledermoscopy images acquired in primary health care and hospital settings - a comparative study of image quality.
J Eur Acad Dermatol Venereol. 2017 Aug 29. doi: 10.1111/jdv.14565. [Epub ahead of print]

IV. Dahlén Gyllencreutz J, Bengtsson Boström K, Terstappen K.
Does it look like melanoma? A pilot study of the effect of sunless tanning on dermoscopy of pigmented skin lesions.
Br J Dermatol. 2013; 168: 867-70

Content

Abbreviations

ALM ..... Acral lentiginous melanoma
AML ..... Atypical melanocytic lesion
AK ..... Actinic keratosis
BCC ..... Basal cell carcinoma
CI ..... Confidence interval
CMN ..... Congenital melanocytic naevus
CN ..... Common naevus
DEJ ..... Dermoepidermal junction
DHA ..... Dihydroxyacetone
DN ..... Dysplastic naevus
DNA ..... Deoxyribonucleic acid
DOR ..... Diagnostic odds ratio
Dx ..... Diagnosis
FTF ..... Face-to-face
IDS ..... International Dermoscopy Society
LED ..... Light emitting diodes
LM ..... Lentigo maligna
LMM ..... Lentigo maligna melanoma
NM ..... Nodular melanoma
NMSC ..... Non-melanoma skin cancer
NPD ..... Non-polarised dermoscopy
PD ..... Polarised dermoscopy
PDA ..... Personal digital assistants
PSL ..... Pigmented skin lesion
RDOR ..... Relative diagnostic odds ratio
RR ..... Relative risk
SCC ..... Squamous cell carcinoma
SCP ..... Standardised care pathway (standardiserat vårdförlopp)
SK ..... Seborrhoeic keratosis
SL ..... Solar lentigo
SSE ..... Skin self-examination
SSM ..... Superficial spreading melanoma
TBP ..... Total body photography
TD ..... Teledermatology
TDS ..... Teledermoscopy
TBSE ..... Total body skin examination
UVA ..... Ultraviolet A radiation
UVB ..... Ultraviolet B radiation
UVR ..... Ultraviolet Radiation

1. Introduction

Skin cancer, a group of tumours consisting mainly of malignant melanoma (melanoma), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), are among the cancers with the largest increase in incidence over the last decades, in Sweden and internationally.[1-4] Dermatologists play an important role in the work with dealing with the increased incidence. With skill in non-invasive methods such as dermoscopy it is possible to detect malignant tumours at an early stage while also lowering the number of benign lesions needing to be excised.[5-7] In Sweden, the most common way of reaching a dermatologist is through a referral, most often sent by a primary health care (PHC) physician. One of the ways the referral is meant to be used is as a triaging tool. Traditionally, referrals are text based and contain no images, making it difficult to differentiate, at the time of triaging, between benign and malignant lesions.

The general aim of this thesis was to study how the use of teledermoscopy affects the care of patients with suspicious skin lesions, from triaging, to establishing a diagnosis and planning treatment. We also aimed to study safety aspects of digital dermoscopy and teledermoscopy as well as to point out risks and pitfalls so that they can be avoided.

1.1 The human skin

The skin covers the external surface of the human body and serves as a barrier that protects internal tissues against damage from external dangers including trauma, heat, and ultraviolet radiation (UVR). It is divided into three layers: the epidermis, dermis and subcutis *(figure 1)*. The epidermis is a stratified, squamous epithelium that consists primarily of keratinocytes. Other cells found in the epidermis include melanocytes, Langerhans cells and Merkel cells. The epidermis contains no blood or lymphatic vessels and is dependent on the underlying dermis for nutrient delivery and waste disposal.

The dermis contains collagen, elastic fibres, blood and lymphatic vessels, sensory structures, and fibroblasts. The dermis is divided into the superficial papillary dermis and the deeper reticular dermis. Nutrients and waste products diffuse between the epidermis and dermis, through the dermoepidermal junction (DEJ). The contact area between the two layers is increased by extensions of the dermis into the epidermis, called dermal papillae. The corresponding parts of the epidermis are called rete ridges. Epidermal appendages are intradermal structures lined with epithelial cells with the potential for division and differentiation. They include sebaceous glands, hair follicles, sweat glands, apocrine glands, and mammary glands.

The subcutis is a layer consisting mainly of loose connective tissue and fat cells. It acts as thermal insulation and further protection from trauma.

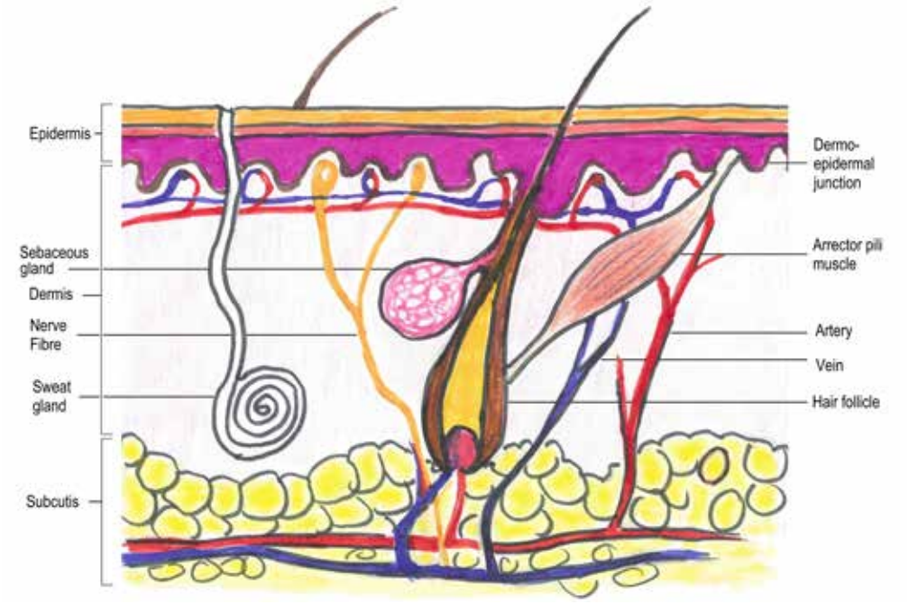


FIGURE 1. Schematic structure of the human skin. ***Artwork:*** *Weronica Dahlén*

1.1.1 Difference in the skin on different body parts

The structure of the skin varies on different parts of the body. This includes the thickness of the epidermis and dermis. The epidermis can be as thin as 0.05 mm on the eyelids and over 1 mm thick on the palms and soles. The dermis' thickness varies between 1 and 10 mm, being thickest on the back. Apart from this, there are specific differences found in facial and acral skin. In the facial skin, the rete ridges are often flattened or absent while there is an increased number of follicular infundibula *(figure 2, left side)*.[8] In the glabrous, acral skin of the palms and soles, the epidermis is thicker than that of non-glabrous skin and there are a large number of eccrine sweat glands but no hair follicles. Another difference is that the underlying structure of the skin causes the surface of the glabrous skin to form furrows and ridges *(figure 2, right side)*.[9]

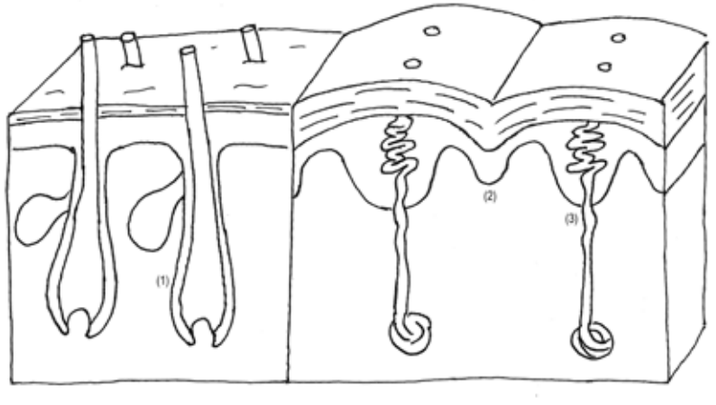


FIGURE 2. Schematic structure of facial skin (left side) with flattened rete ridges and multiple follicles (1), and acral skin (right side) with furrows over the crista profunda limitans (2) and ridges over the crista profunda intermedia (3), where the sweat duct also exits.
Artwork: *Johan Dahlén Gyllencreutz*

1.1.2 Optical properties of the skin

The skin has a different density and refractive index than the air and this causes much of the light that reaches the skin to be reflected. This can prevent the clear viewing of structures in the epidermis and dermis. Light that enters the skin can be absorbed, scattered, or reflected. When viewing the skin and lesions of the skin, only the light that is remitted from the epidermis and dermis is of use.[10]

1.1.3 Melanocytes and tanning

Melanocytes are dendritic cells that produce melanin, a pigment which protects the skin from the harmful effects of UVR. Melanin accumulates in organelles called melanosomes that can be transferred to the surrounding keratinocytes where they remain as granules. Melanocytes are found in the basal layer of the epidermis as well as in hair follicles, the retina, uveal tract, and leptomeninges. Absolute numbers of melanocytes are the same among the various skin types. Thus, differing pigmentation among individuals is related to melanosome size and activity rather than cell count.

Sun exposure, melanocyte-stimulating hormone, adrenocorticotropic hormone, oestrogens, and progesterones stimulate melanin production. Melanin is divided into the brown-black eumelanin and the yellow-red pheomelanin. The photoprotective properties of melanin are accredited mainly to eumelanin, while pheomelanin is thought to cause a harmful effect after UVR exposure, by generation of free radicals.[11-13]

UVR-induced tanning occurs in two phases. An immediate pigment darkening is caused by Ultraviolet A radiation (UVA, 315-400 nm) by oxidation and redistribution of existing melanin, this effect fades after hours to days and does not appear to protect against sunburn. Delayed tanning is visible 24 to 72 hours after exposure to UVA and Ultraviolet B radiation (UVB, 280-315 nm) and is caused by increased synthesis of epidermal melanin. Another natural effect of UVB exposure is a thickening of the skin (primarily the stratum corneum) that, together with the increased pigmentation, helps to protect from sun damage. The ability to tan or tendency to burn after UVR exposure is the basis of the classification of skin types according to the Fitzpatrick scale.[14] *(Table 1)*

TABLE 1. Fitzpatrick scale.

Skin type	Reaction to UVR exposure
I	Always burns, never tans
II	Burns easily, tans poorly
III	Burns moderately, tans, sometimes after a slight burn
IV	Burns minimally, tans easily
V	Rarely burns, tans darkly easily
VI	Never burns, always tans darkly

UVR, ultraviolet radiation

1.2 Benign Skin Lesions

There are several kinds of lesions naturally found in the human skin. In many cases these lesions cause little or no problems but sometimes they are a cause of concern for patients, resulting in them seeking health care. Without proper diagnostic methods and training, it can be difficult to differentiate these benign lesions from malignant ones (see section 1.3). This contributes to the fact that benign skin lesions lead to a substantial number of visits in PHC and dermatology departments as well as to a large number of biopsies and excisions. In Sweden, the number of benign naevi excised for every melanoma has been calculated to 58, making the

management of skin lesions expensive and putting a strain in the limited recourse of dermatopathology.[15]

Some of the most common benign lesions will be listed here.

1.2.1 Melanocytic lesions

Common naevus

Common naevi (CN) are made up of proliferations of melanocytes, typically located in nests at the DEJ or in the dermis. In an individual, the number of CN generally increases during the first three to four decades of life and later the numbers tend to decrease.[16] The number of CN in an individual is associated with the naevus count of the parents, pigmentation traits/skin type as well as sun exposure and sunburn in childhood.[17] There is a possibility of a CN transforming into a melanoma but the risk of this is considered very low. In a study by Tsao et al. it was found that the life-time risk of transformation of a single naevus into melanoma was about 1/3,000 for men and 1/10,000 for women. The highest annual risk of transformation was found in men aged over 60, and was 1/30,000.[18] A high number of naevi is nonetheless seen as a risk factor for developing melanoma, with individuals having more than 120 naevi approaching a relative risk (RR) of 10.[19]

Traditionally, CN are classified histologically based on where melanocytic nests are found in the skin, as junctional naevi (with melanocytes mainly located at the DEJ), compound naevi (with melanocytes located at the DEJ as well as in the dermis), and intradermal naevi (with melanocytes mainly located in the dermis. Examples of naevi can be seen in *figure 3*.

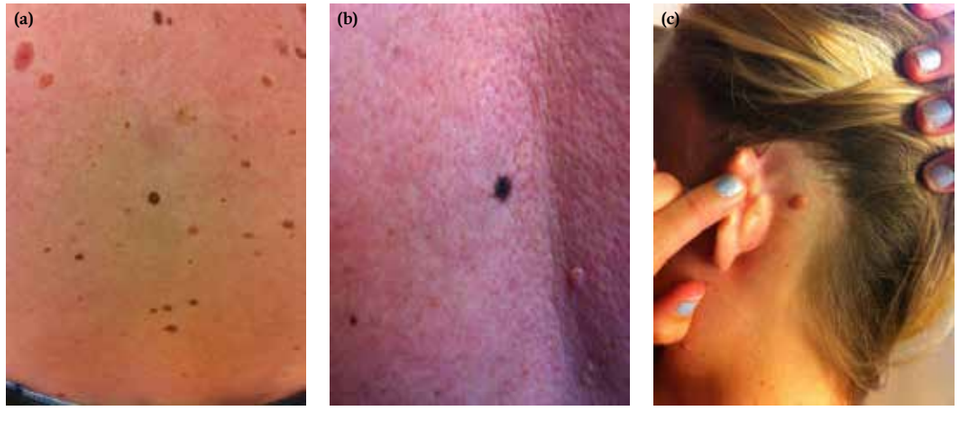


FIGURE 3. Clinical presentation of naevi. (a) Multiple naevi with varying size and colour, (b) a dark, flat naevus and (c) a raised, intradermal naevus. ***Photo:*** *Johan Dahlén Gyllencreutz*

Congenital melanocytic naevus

The definition of a congenital melanocytic naevus (CMN) is that it is present at birth or appears during the first two years of life. CMN are divided into groups based upon the predicted size in adulthood, into small (<1.5cm), medium (1.5-<20cm), large (20-<50cm) and giant (>50cm) CMN. Although CMN are benign, there is an increased risk of malignant transformation for large and giant CMN, being as high as 14% in individuals with CNM with a projected adult size of >60cm.[20] In this group about 70% of melanomas occur before the age of 10 years, often in the CMN but sometimes extracutaneously in the CNS.[21]

Blue naevus

A variant of benign naevus where there are dendritic melanocytes found in the upper and mid dermis. Most commonly a homogenous blue colour is seen *(see figure 4a)* but there are a number of less common variants, including white blue naevi with less pigment and polychromatic blue naevi in which more than one colour is seen.[22] These lesions are stable and do not grow, something that can help differentiate them from malignant lesions, including melanoma and cutaneous metastases of melanoma. The presence of black colour should also cause suspicion of melanoma.[23]

Spitz naevus

This type of naevus exists in a pigmented and a non-pigmented variant, the former including the type called Reed naevus *(figure 4b and c)*. Although benign, Spitz naevi and melanoma can be very similar, and because of this many recommend that this type of naevus is always excised, especially if the lesion is raised or appears after puberty.[24]

Dysplastic naevus

Histopathologically, the term dysplastic naevus (DN) is used for melanocytic naevi that exhibit defined structural features that can differentiate them from CN, as well as different degrees of cellular atypia (mild, moderate, or severe). The agreement between pathologists regarding the histopathologic diagnosis of DN varies but is low for grading cellular atypia.[25-27] In contrast to histopathologically proven DN, the term DN used in a clinical setting should be avoided.[28, 29] When clinically atypical melanocytic lesions are excised they often do not exhibit the features of DN, and vice versa.[30, 31] An example is seen in *figure 4d*.

Historically, DN were considered precursors to melanomas, but there is no evidence to support this theory.[28, 29, 32] In studies on naevi transforming into melanoma, the naevi found associated with cases of melanoma have been CN at least as often as DN. Also, most melanoma were found to occur without an associated naevus.[33-35] The term DN is sometimes still used in clinical practice to indicate difficulties to differentiate between a naevus and early melanoma. In these cases, the term atypical melanocytic lesion (AML) could be more appropriate as the nature of the lesion is unknown at the time of evaluation.[36]

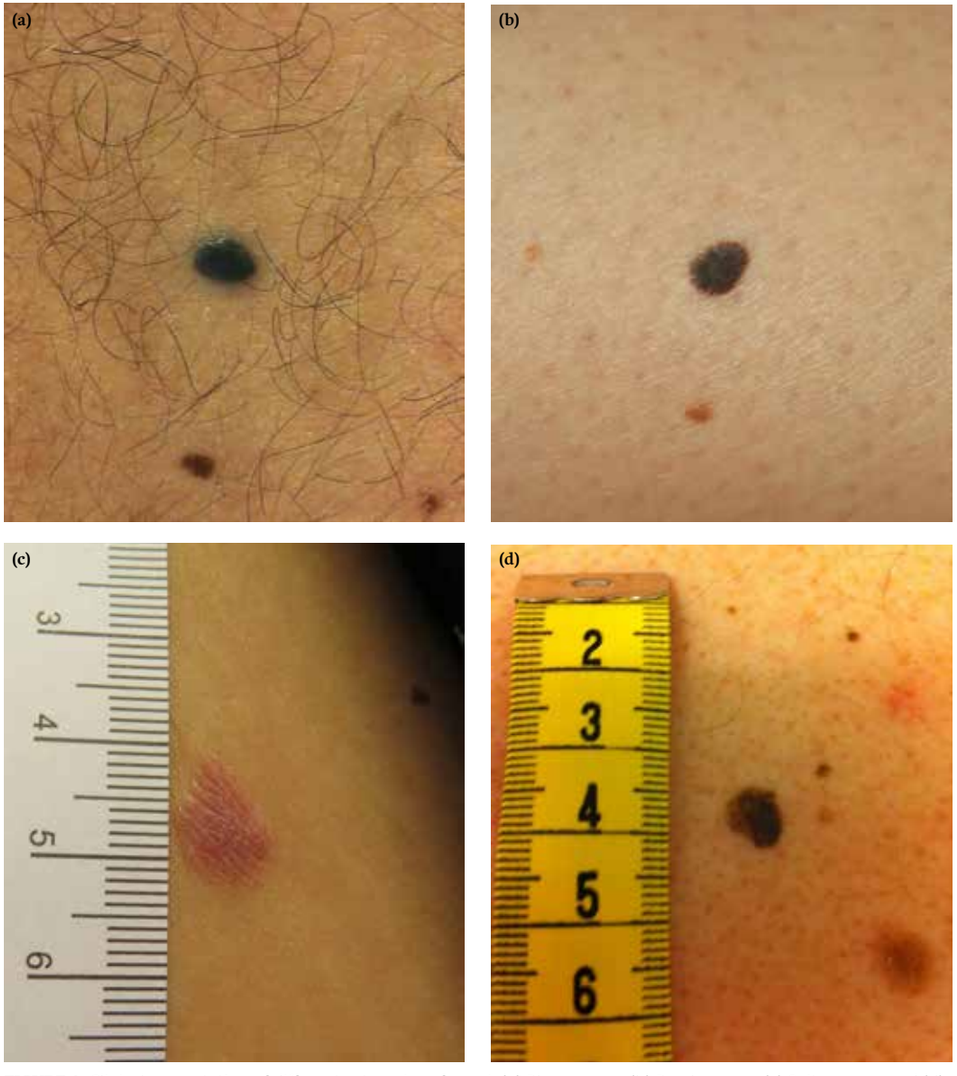


FIGURE 4. Clinical presentation of different categories of naevi. (a) Blue naevus, (b) Reed naevus, (c) Spitz naevus and (d) histopathologically confirmed dysplastic naevus.
Photo: *John Paoli (a-c), and Johan Dahlén Gyllencreutz (d)*

1.2.2 Non-melanocytic lesions

Seborrhoeic keratosis

Seborrhoeic keratosis (SK) is a very common type of benign lesion that most individuals develop during their lifetime. Numbers vary between individuals and generally increase with age. They are often raised lesions with colours ranging from yellow to brown-black and are made up of epidermal keratinocytes *(figure 5a)*.[37] In many cases these lesions are easily recognised but they can sometimes imitate malignant diagnoses due to the presence of multiple colours and structures, especially when inflamed or traumatised. When managed by non-dermatologists, this type of lesions can lead to a large number of surgical procedures.[38] It is possible to divide SKs into different subtypes, e.g. acanthotic, hyperkeratotic and reticulated variants.[39]

Solar lentigo

Another very common benign lesion, usually found on chronically sun-damaged skin is solar lentigo (SL). These lesions are usually flat, light brown to black, and made up of keratinocytes that are pigmented by melanin. They can remain as SL or develop into reticulated SK. This type of lesion often occurs in the face and sometimes it can be difficult to differentiate between SL and other facial lesions, including lentigo maligna (LM) and pigmented actinic keratosis (AK).[8, 40]

Dermatofibroma

Dermatofibroma is yet another common, benign skin lesion that can occur anywhere but are more commonly found on the upper and lower extremities. The cause of a dermatofibroma is unknown, but inflammatory responses to trauma, folliculitis and insect bites have been considered as well as regarding it a neoplasm.[41] Dermatofibromas are made up of fibroblasts and collagen fibres. They are usually firm lesions with a sclerotic centre and pigmentation in the periphery *(figure 5b)*. Lateral pressure on these lesions can produce a depression of the skin, called the “dimple sign”. Sometimes itching makes the patient aware of the lesion.[42]

Cherry angioma and angiokeratoma

Cherry angiomas are a common type of skin lesion, made up of blood vessels. They are usually small, red to purple, sharply demarcated lesions, which appear in adults and are usually easily recognised *(figure 5c)*.[43, 44] If thrombosed, the colour can be darker or even black, sometimes causing concern. Angiokeratomas are similar lesions, made up of telangiectatic vessels in the papillary dermis with an overlying thickened epidermis and stratum corneum. They can have a more scaly surface and red to black colour.[45]

Pyogenic granuloma

Pyogenic granuloma is a relatively common vascular lesion usually presenting as a nodule with a red or ulcerated surface.[46] They are benign lesions, sometimes developing after a small trauma to the skin. However, both the often-rapid growth and clinical presentation of these lesions can make it difficult to completely exclude malignancy and removal for histopathological diagnosis it therefore recommended. It is also common for pyogenic granulomas to cause discomfort and profuse bleeding.

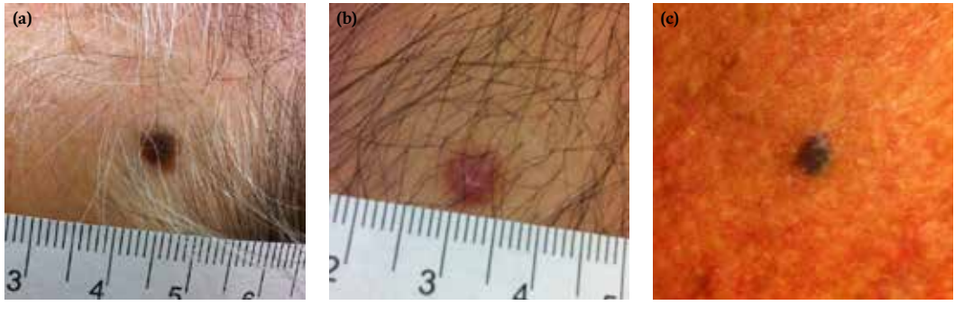


FIGURE 5. Clinical presentation of benign, non-melanocytic lesions. (a) Seborrhoeic keratosis, (b) dermatofibroma and (c) cherry angioma. ***Photo:*** *Johan Dahlén Gyllencreutz*

1.3 Skin Cancer

The three most common types of skin cancer are melanoma, SCC, and BCC. Melanoma is derived from melanocytes, whereas SCC and BCC are derived from keratinocytes. The latter two are therefore classified within the group of cancers called non-melanoma skin cancer (NMSC), also called "keratinocyte cancer". There has been a marked increase in the incidence of melanoma and NMSC during the last decades, in Sweden and internationally.[1-4] Less common types of NMSC (e.g. dermatofibrosarcoma protuberans, Merkel cell carcinoma or sebaceous carcinoma) are not covered in this thesis.

1.3.1 Malignant melanoma

The major reason for dedicating time and effort into an improved management of skin lesions is the diagnosis of melanoma, as this is by far the most malignant of the common types of skin cancers. Melanoma generally arise from melanocytes in the epidermis but can occur in other organs where melanocytes are present e.g. the leptomeninges or the retina. Melanoma usually presents as a growing, asymmetrically pigmented lesion with more than one colour *(examples seen in figure 6)*. While they eventually become detectable with the naked eye, early melanomas can be difficult to differentiate from naevi. In about 70% of cases, melanoma arise de novo, i.e. from individual melanocytes, while in about 30% of cases, there is a pre-existing naevus.[33-35] Melanoma in situ is a case of melanoma that has not yet invaded the dermis but can develop into invasive melanoma at any given time, lentigo maligna (LM) being a more slowly progressing variant appearing on chronically sun-damages skin.

As stated above, the incidence of melanoma has increased substantially during the last decades, in Sweden and internationally.[2] In Sweden, it has become the fifth most common type of cancer (excluding BCC) for women and the sixth most common for men. In 2015, 3,951 cases of melanoma were reported, 1,925 cases occurring in women and 2,026 cases occurring in men. There were also about 3,000 cases of melanoma in situ reported, but that number should be viewed with caution, as lesions with the histopathologic diagnosis of DN with severe dysplasia are included.[47] The incidence of melanoma in Sweden has increased annually with about 5% during the last decade and is now 36.3 per 100,000 individuals for women 41.6 per 100,000 for men (Swedish Standard population year 2000).[48] The mortality of melanoma has increased but remains low. In 2015, 514 people in Sweden died because of melanoma (192 women and 322 men).[49]

Mortality from melanoma is affected by several patient and tumour-related factors.[50, 51] The most important prognostic, tumour-related factor for melanoma that has not metastasised, is the tumour thickness measured in millimetres according to Breslow (measured from the stratum granulosum to the deepest malignant cell). If excised early, when the tumour is thin, most patients can be cured; while in patients with thick melanoma, the prognosis is poor. The 10-year survival rate in melanoma with a thickness of 1 mm or less has been found to be 92%, compared to 50% for melanoma with a thickness of over 4 mm.[50] In studies on melanoma growth rate, it has been calculated that the Breslow thickness can increase with 0.05 to 0.5 mm per month, depending on the type of tumour.[52, 53] It is therefore vital that melanoma is diagnosed as early as possible, to be able to treat patients before the disease spreads. Although recently discovered immunotherapy drugs have shown promising results and improved overall survival for metastatic melanoma,[54] a cure for spread disease is not available.

Cutaneous melanoma can be classified into groups based upon histopathology and location, into the most common superficial spreading melanoma (SSM); the more aggressive nodular melanoma (NM); lentigo maligna melanoma (LMM) appearing on chronically sun-damaged skin in older patients and acral lentiginous melanoma (ALM) located on the hands, feet or under the nails.[55] It is also possible to divide melanoma based upon growth rate into: thin with a slow growth rate; thin with an intermediate growth rate and thick with a fast growth rate.

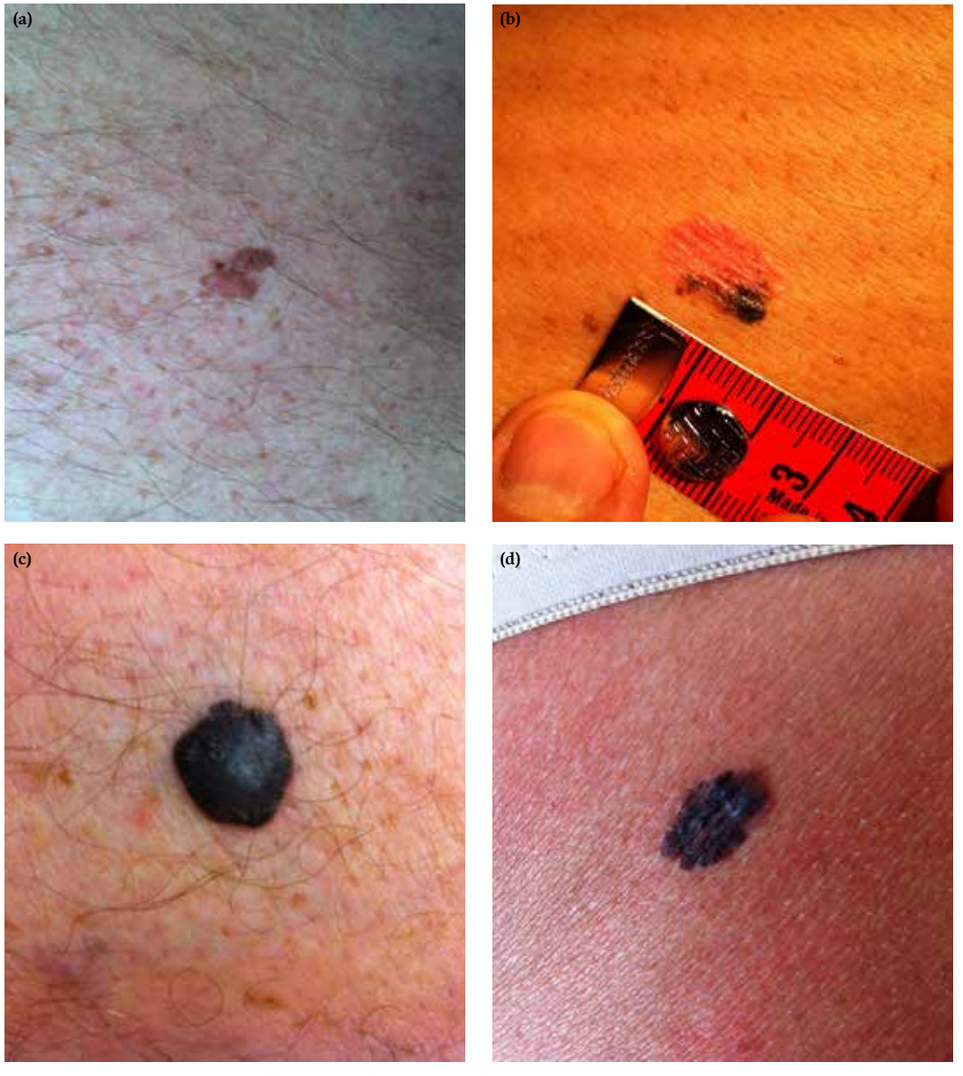


FIGURE 6. Clinical presentation of four cases of melanoma. (a) Melanoma in situ showing brown and red colour and an asymmetric shape. (b) Red and black melanoma, larger than one centimetre. (c) Nodular melanoma that is raised and dark but symmetric in shape and colour. (d) Melanoma with black and grey-blue colour. ***Photo:*** *Johan Dahlén Gyllencreutz*

1.3.2 Non-melanoma skin cancer

Non-melanoma skin cancer, as a group, is the most common of all malignancies in populations with lighter skin types. Nevertheless, exact numbers remain unclear as many countries do not report NMSC cases, or do so only partially.[4, 56] As mentioned earlier, there are many uncommon types of NMSC, but this thesis will focus on SCC and BCC, which are by far the most common types.

Squamous cell carcinoma and precursors

Squamous cell carcinoma is the less common but more serious of the two cancers brought up here. SCC can present as a growing, red or pink nodule with scales, crusts, and/or ulceration *(figure 7c)*. Like melanoma, the incidence of SCC has increased rapidly during the last decades in Sweden, where it is now the second most common type of cancer (excluding BCC) in both women and men.[1] In 2015, 6,826 cases of SCC were reported with 3,932 in men and 2,894 in women. The incidence rates were 88.8 per 100,000 for men and 48.6 per 100,000 for women (Swedish Standard population year 2000).[48] As SCC is usually slow to spread, the mortality is much lower than for melanoma. In 2015, 71 people died in Sweden because of SCC (41 men and 30 women).[49]

It is possible to divide SCC into groups, based on how differentiated the tumours are: well, moderately and poorly differentiated. Higher risk of metastasis is seen in poorly differentiated tumours, SCC located on the lip or ear, and large or deeply invading tumours.[57, 58] Keratoacanthoma is a variant of well differentiated SCC, which has the potential to regress but that cannot be completely differentiated from regular SCC.

When SCC has not yet invaded the dermis, but presents as intraepidermal dysplasia throughout the full thickness of the epidermis, it is called SCC in situ or Bowen's disease. These lesions usually present as red plaques with scales *(figure 7b)*. The risk of progression to invasive SCC is estimated to 3-5%.[59] Another very common, potential precursor for SCC is actinic keratosis (AK) in which the atypical keratinocytes don't occupy the full thickness of the epidermis. AKs may be solitary but often present as multiple, thin, red lesions with scales. A number of variants exist, including the less common pigmented type that can sometimes mimic LM. AKs sometimes cover large portions of chronically UVR-exposed skin, a concept called field cancerisation *(figure 7a)*. The risk of progression to invasive SCC is estimated to be about 10% over a period of 10 years but lesions can often remain unchanged or even regress.[60, 61]

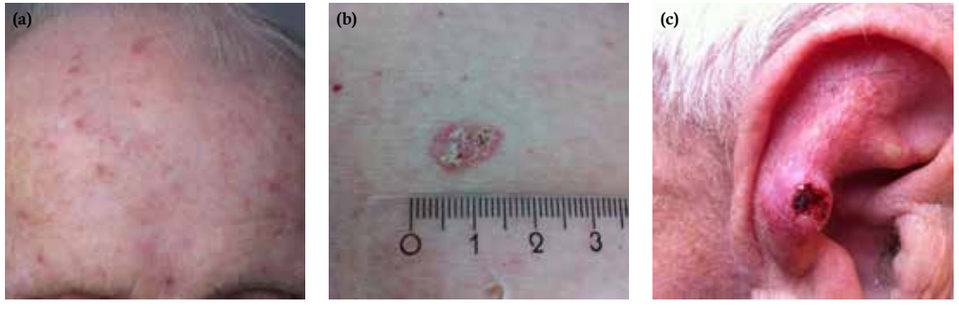


FIGURE 7. Clinical presentation of squamous cell carcinoma (SCC) and precursors. (a) Multiple actinic keratoses on the forehead and scalp. (b) SCC in situ with more infiltration as well as hyperkeratosis. (c) Invasive SCC showing an ulcerated, pink, nodular lesion on the ear. ***Photo:*** *Morgan Carlsson (a) and Johan Dahlén Gyllencreutz (b-c)*

Basal cell carcinoma

Basal cell carcinoma is the most common type of NMSC and the most common malignant tumour of all in many countries. However, as the risk of metastasis is almost non-existent, these tumours are not always reported or included in national cancer statistics.[4, 56] In Sweden, 46,727 cases of BCC were reported by pathologists in 2015. This is a low estimate, as clinicians do not report BCCs and many tumours are treated with non-surgical methods, without prior biopsy. BCC can have different presentations *(figure 8a-c)*. Nodular BCCs most commonly present as a shiny, pink to red nodule with or without ulceration, whereas superficial BCCs manifest as a red plaque with small erosions and sometimes a slightly more raised border.

There are different ways of classifying BCCs. In Sweden, the Glas classification (Sabbatsberg classification) is often used,[62] splitting the BCCs into the following clinicopathological subtypes: nodular (Glas type Ia), superficial (Glas type Ib), intermediately aggressive (Glas Type II) and highly aggressive (Glas Type III, including the morphoeic subtype). Although not associated with any substantial mortality, the tumours can grow locally and can cause tissue damage to the skin and underlying structures. A smaller proportion of BCCs are pigmented and in some cases melanoma can be a differential diagnosis.[63]

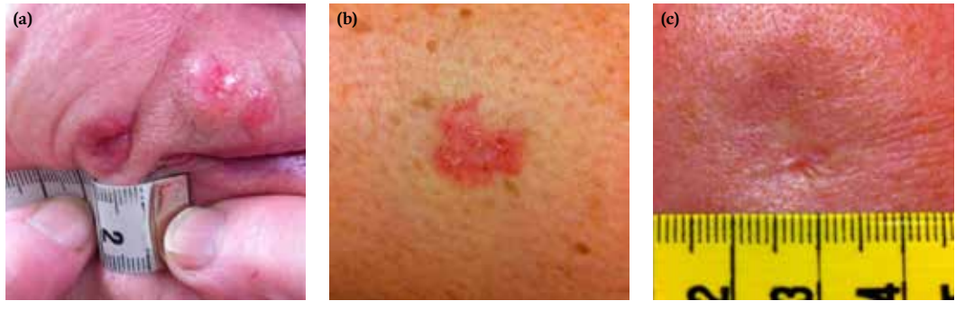


FIGURE 8. Clinical presentation of basal cell carcinoma (BCC). (a) Nodular BCCs on the lip and cheek, which are pink with a shiny surface and visible vessels. (b) Superficial BCC showing white-red areas and small ulcerations. (c) Aggressive BCC, morphoeic variant, with a scar-like appearance. ***Photo:*** *Johan Dahlén Gyllencreutz*

1.3.3 Aetiology

Environmental factors

The most important external risk factor of skin cancer is exposure to UVR, which is true for both melanoma and NMSC.[64, 65] Both UVA and UVB, the two types of natural UVR that reach the earth's surface, increase the risk of skin cancer. UVB causes direct DNA damage such as the creation of cyclobutane pyrimidine dimers that, if not repaired correctly, cause mutations. Meanwhile, UVA causes more indirect damage by formation of free radicals and reactive oxygen species.[66, 67] The risk of SSM appears to have the strongest association with intermittent UVR exposure and painful sunburns, especially in childhood, while LM/LMM is more associated with chronic UVR exposure. For NM and ALM the association with UVR is not well defined.[64] Chronic UVR exposure appears to be related to a higher risk of SCC and its precursors while the association with BCC is less clear-cut. BCCs often develop in areas of chronic UVR exposure but also seem to be

associated with intermittent UVR exposure.[68] An increased risk of melanoma and NMSC is related not only to exposure to UVR from the sun but also to UVR from tanning beds, especially if used at an early age.[69, 70] Medically used UVR in the form of PUVA (psoralen + UVA) has also been associated with an increased risk of skin cancer.[71, 72] Other environmental risk factors include ionising radiation [73] and immunosuppression.[74]

Host factors

Host factors that increase the risk for skin cancer in general include fair skin, red or light coloured hair, light coloured eyes and the inability to tan.[75, 76] The risk of melanoma is also increased in patients with a large number of naevi and multiple large naevi,[19, 77, 78] as well as in those with a family history or personal history of melanoma.[75, 79-82] The highest risk of all for melanoma exists in patients with specific mutations, the most common being in the CDKN2A gene.[83] Other genetic disorders that increase the risk of skin cancer include xeroderma pigmentosum, a disorder conveying an inability to repair UVR-induced DNA damage thereby increasing the risk of NMSC and melanoma;[84] as well as Gorlin's syndrome, which is caused by a mutation that substantially increases the risk of multiple BCCs.[85]

1.3.4 Treatment

Most cases of melanoma and NMSC can be managed without the need of systemic treatment. When treatment is completed at an early stage it is often possible to cure the patient, even if the diagnosis is melanoma. If performed late, when the cancer has metastasised, the prognosis is generally very poor, especially in the case of melanoma. Treatment of advanced disease is not included in this thesis.

For many malignant and premalignant skin lesions, surgical excision is considered the gold standard. It is, with a few exceptions, the only recommended option for melanoma, melanoma in situ, SCC, and the most aggressive forms of BCC. Guidelines state the recommended excision margins for the different tumours.[86-90] A major advantage of surgical excision is that the tissue excised can undergo histopathological investigation, to verify the diagnosis and that the removal of the tumour is complete.[91] A regular elliptical excision is the most common method but a more advanced surgical technique called Mohs micrographic surgery can also be used. With this method, the tissue removed is frozen and sectioned, so that the complete surgical margins can be examined histopathologically immediately after the excision, allowing for precise mapping of any remaining tumour cells. In the case of positive margins, further stages of surgery are performed until the lesion is completely removed. This method achieves lower recurrence rates when treating locally aggressive tumours, while minimising the removal of healthy tissue.[92] In Sweden, Mohs micrographic surgery is mostly used for the treatment of highly aggressive or recurrent BCC in the facial area.[93]

Non-surgical treatment is also used, especially when there are multiple precancerous lesions or less aggressive lesions located where surgery is more difficult (e.g. nose and ears). Cryosurgery, with or without curettage, implies the use of liquid nitrogen to cause cell death and tumour destruction for the treatment of superficial and nodular BCC, SCC in situ and AKs.[94-97] Photodynamic therapy, a method using a photosensitiser (usually 5-aminolaevulinic acid, or methyl aminolaevulinate) together with subsequent illumination specific wavelengths of light to cause tumour-specific cell death, can be used for superficial tumours (e.g. superficial BCC, SCC in situ and AKs).[98] Curettage and electrodesiccation aims to destroy residual tumour cells and reach haemostasis by debulking the tumour with curettage and then dehydrating the wound bed with a high-voltage, low-amperage electrical current through an unheated electrode. This is used mainly for non-aggressive BCCs and SCC in situ.[99] Finally, there are several topical treatments (fluorouracil, imiquimod, ingenol mebutate, and others) mostly used for the treatment of AKs.[100]

Surgical treatment clearly has benefits. However, it generally requires more time than is allocated for a patient seeking health care for a skin lesion of concern. Because of this, it is not always possible to perform surgery at the first visit, even when such treatment is found to be necessary. This can result in multiple visits as well as a delay before primary treatment is completed.

1.3.5 Prevention

To turn the trend of increasing skin cancer incidence, preventive measures are called for. In medicine, including dermatology, prevention can be divided into three levels. Primary prevention has the goal of decreasing the risk of disease occurring in the first place. Secondary prevention aims at early detection of often asymptomatic disease, to be able to treat it before it has progressed and resulted in major morbidity. Finally, tertiary prevention deals with reducing the negative impact of disease that is already present. In the following section primary and secondary prevention related to skin cancer will be briefly brought up.

Primary prevention

Primary prevention related to skin cancer is focused on decreasing the exposure to UVR, in the population in general, or in selected groups, such as children or outdoor workers. The focus is often on preventing melanoma. Measures taken can include making sure there is shade at playgrounds and beaches, educating the public about UVR and skin cancer, promoting the use of protective clothing and sunscreens or limiting the availability of tanning salons by legislation. Among the most known and ambitious programs is Australia's SunSmart program which has focused on a large number of areas including attitudes toward tanning, sun protection, sun exposure of children etc.[101] This program may have contributed to the tendency for more stable or lower incidence of melanoma during the recent years.[102] Such a tendency has not been seen in Sweden. A potential part of primary prevention could be the promotion of sunless tanning options such as products containing dihydroxyacetone (DHA), discussed below, in section 1.3.7.

Secondary prevention

Secondary prevention of skin cancer includes educating patients on when they need to seek health care for skin lesions or to perform skin self-examinations (SSE). Also, having dermatologists and other physicians perform examinations to catch early, hopefully curable, cases of skin cancer, primarily melanoma. This includes when it is done for asymptomatic patients, i.e. screening.

Patients often detect primary or recurring melanoma themselves and education might improve this further and lead to melanoma being detected earlier.[103] Although there is not enough data to state how SSE affects mortality in skin cancer, one study on the effect of SSE found an indication of a lower risk of melanoma in the patients that performed SSE, as well as lower risk of

advanced disease among melanoma patients in this group. One implication of the results was that SSE could potentially decrease melanoma mortality by 63%.[104] It has also been found that while melanoma is often detected by patients, the ones detected by physicians are often thinner, therefore having a better prognosis.[105] To actively search for melanoma in the population therefore seems appropriate, i.e. to perform screening. While there is not enough evidence for mass screening of the entire population[106] other forms of screening may be more appropriate. Skin cancer screening by dermatologists in Sweden is focused on patients belonging to specific risk groups such as familial melanoma or organ transplant patients. Given that skin cancer is the second most common cancer for men and women in Sweden, opportunistic screening by performing a total body skin examination (TBSE) in PHC should also be recommended. This has been found to be beneficial for some groups, including older patients, patients with previous NMSC and those who seek health care for a skin tumour.[107]

1.3.6 Attitudes

Exposure to UVR is unavoidable and has positive effects (including production of vitamin D) that take place at the same time as the DNA damage.[108] It is more problematic when there is an overexposure to UVR. This sometimes occurs as a "side effect" of outdoor work or recreational habits, but is sometimes a result of intentional UVR exposure, with the specific goal of achieving a tan. A tanned appearance is often viewed as something positive, a sign of health and a part of good physical appearance. In fact, Sweden is among the countries where the drive to reach a tanned skin is the strongest and the tendency to use sun protection is the lowest.[109, 110] This attitude towards tanning can be associated with a higher degree of UVR exposure, including the use of tanning salons.[111, 112] Melanotan I and II are other agents that are sometimes used by people with a strong desire for tanned skin. They are synthetic analogues of α-melanocyte-stimulating hormone that are administered by subcutaneous injection, sometimes followed by UVR-exposure, resulting in a substantial pigmentation of the skin. These substances are not licensed for this use and must therefore be obtained illegally. Melanotan has in case reports been associated with eruptive naevi, atypical naevi, and melanoma.[113-115]

As changing these attitudes is likely hard and time-consuming, a UVR-free alternative to achieve a tan is desirable.

1.3.7 Dihydroxyacetone and sunless tanning

One such alternative exists in the form of sunless tanning products containing dihydroxyacetone (DHA, $C_3H_6O_3$). DHA is a three-carbon, vegetable-derived sugar that is colourless, but that interacts with amino acids in the keratinocytes in the stratum corneum, through a process called the Maillard reaction. Brown-black chromophores called melanoidins are developed, giving the tanned appearance. The pigmentation appears after a few hours, reaches its peak within a day, and decreases during about a week with the normal shedding of the skin. The tanning properties of DHA have been known since the 1920s and have been marketed for this purpose since the 1950s.[116]

DHA has been found to be a safe way of achieving a tan and gives a small protection against UVR.[117, 118] Negative effects that have been brought up in studies are rare occurrences of contact dermatitis[119] and the increased formation of free radicals in the skin if DHA application is followed by immediate UVR exposure.[120]

The number of studies on how the use of DHA relates to sun behaviour/UVR-exposure or skin cancer are still limited. One study found an association between the use of DHA and reporting severe sunburns and use of tanning beds. This was considered an alarming finding but might also indicate that those who feel that it is important to be tanned are ready to use different methods to achieve this. Another study, where individuals who underwent spray-on sunless tanning were asked about UVR behaviour, found that many were ready to replace tanning bed use but not exposure to natural UVR with the use of DHA.[121] Another survey-based study found that the desire for tanned skin was strong and that just under 40% of users of sunless tanning products reported a decreased frequency of tanning in the sun and in tanning beds.[122] In 2006, a study was conducted where two beaches were randomly selected, one to an active intervention and another to control. From these beaches a total of 250 women were included. The active intervention included information about sunless tanning and the recommendation to use such products as an alternative to sunbathing. Information about skin cancer was included, as well as a UV-filtered photograph, the latter intended to show signs of sun damage. The participants in the control group had their picture taken with an instant camera and were told they would be contacted at a later date. All participants were contacted after 2 months and one year, to answer surveys. In the intervention group of 125 women they found a short-term decrease in sunbathing, sunburn and an increase in use of protective clothing, while long-term effects were a decrease in sunbathing and increase in use of sunless tanning.[123] Although there is not enough data to clearly state how use of and promotion of sunless tanning affects skin cancer, it remains as an alternative to the much more harmful overexposure to UVR.

One aspect that is not well studied is how the use of DHA affects dermoscopy (see section 1.4). Only a few short articles exist related to DHA use and dermoscopic features. A case report by Martin et al. reported dermoscopic changes in CN and SKs after the use of DHA.[124] Others have also reported similar findings, in 1-3 patients with CN or SKs.[125, 126] Another short article described how sunless tanning use could give rise to the appearance of a parallel ridge pattern on acral skin, mimicking ALM.[127] These papers indicate that dermoscopic features can be affected by DHA use, something that can make it less appropriate to recommend these products to patients followed at dermatology departments. Further studies are needed if this is to be clarified, study IV in this thesis being one such study.

1.3.8 Management and economics

Apart from causing morbidity and mortality, the increasing incidence of skin cancer also results in direct and indirect costs to society that can be substantial.[128, 129] In Sweden, the total costs for skin cancer in 2011 was estimated to €177.6 million, €93 million being related to melanoma. The costs have increased with 27% since 2005.[130] The management of skin tumours differ a great deal between different countries, based on such aspects as the availability of dermatologists, the role of PHC, local traditions, the costs, and reimbursement agreements.

In Sweden, patients with skin lesions of concern are generally seen in PHC and are then referred to dermatologists if there is suspicion of malignancy. In the larger cities, the possibility to see a dermatologist directly

is likely to be higher but most patients still follow the same route. Sometimes surgical treatment of suspicious lesions is performed in PHC or by sending the referral to a general/plastic surgeon. However, in these instances the benign to malignant ratio is often very high, increasing the costs and putting a lot of strain on the limited resource of dermatopathology. By increasing the role of the dermatologist in the management of skin cancer resources could be saved.[15]

Triaging of referrals in Sweden

Triaging of referrals is an important concept to understand when reading this thesis. In Sweden, there are guidelines that state the maximum waiting times to see a dermatologist, depending on the type of skin lesion. These guidelines have changed since the studies included in this thesis were conducted. Specifically, the guidelines for melanoma have changed as Sweden implemented a system called "standardiserat vårdförlopp" (SVF), which could be translated into "Standardised Care Pathway" (SCP).

The SCP for melanoma was introduced in 2015, specifying the maximum time for each step of the management of melanoma, from referral to treatment and follow-up. In many regions of Sweden, the decision to start SCP is made in PHC and dermatologists then need to make sure there are open time slots for all patients sent by SCP referral. In Region Västra Götaland, where the studies included in this thesis were performed, SCP is initiated by a dermatologist, and the maximum times are calculated from that starting point. In the context of SCP, TDS could play a major role, making sure that the right patients are managed swiftly while not allowing unnecessary visits for benign lesions to lead to increased pressure on dermatology departments. The guidelines before and after the implementation of SCP are seen in *table 2*.

TABLE 2. Guidelines for skin lesions, before and after implementation of SCP.

Priority (maximum waiting time)	Included diagnoses, old guidelines	Included diagnoses, new guidelines
SCP (7 days to competed surgery)	-	Melanoma, Melanoma in situ
High (2 weeks)	Melanoma, SCC	SCC
Medium (4 weeks)	Melanoma in situ, SCC in situ	SCC in situ
Low (8-12 weeks)	BCC, AK, AML	BCC, AK, AML
Unprioritised (no FTF visit needed)	CN, SK, Angioma, Dermatofibroma	CN, SK, Angioma, Dermatofibroma

FTF, face-to-face; SCC, squamous cell carcinoma; BCC, basal cell carcinoma; AK, actinic keratosis; AML, atypical melanocytic lesion; CN, common naevus; SK, seborrhoeic keratosis.

1.4 Dermoscopy

1.4.1 Introduction and history

Unlike most types of cancer, skin cancer is externally visible, without the need of radiological examinations or invasive methods. Some cases of skin cancer are clearly seen with the naked eye but at times it is difficult to differentiate between skin cancer and the benign lesions mentioned in section 1.2. Dermoscopy (a.k.a. dermatoscopy, skin surface microscopy, in vivo skin surface microscopy, epiluminescence microscopy or magnified oil immersion microscopy) is the most commonly used, non-invasive method for evaluating skin lesions.

There are descriptions of the use of skin surface microscopy going back to the 17th century. The first use of this method is reported to have been by Peter Borelus and Johan Christophorus Kolhaus to view nailfold capillaries.[131] Since then, different structures or diseases have been studied this way, a few examples being especially worth mentioning. In 1893, Paul Unna was the first to report the use of fluids and oils to make the skin more translucent, a practice still used today.[132] In 1921, although focusing on different applications for dermoscopy, Johann Saphier also studied melanocytic naevi and was the first to describe a dermoscopic structure in the form of globules.[133-136] He also for the first time used the term "dermatoscopy". In the 1950s, Leon Goldman performed further studies on different skin conditions and also studied melanocytic naevi and melanoma. He used different devices, as well as different levels of magnification and different types of light (including polarised light and UV-light) and acquired dermoscopic images.[137] He also developed the first portable dermoscope.[138] In 1972, Rona MacKie showed the advantage of using skin microscopy in differentiating between benign and malignant skin lesions, findings that hold true to this day.[139] The first hand-held dermoscope was designed by Otto Braun-Falco and co-workers in 1989.[140] Since then, further development has been done, improving the light sources with LEDs among other innovations, but to a large extent the principles remain the same. The one major addition is the use of polarised light dermoscopy in the 2000s, removing the need for immersion fluids and contact between the dermoscope and the skin.[141]

1.4.2 Principles and type of light

By magnification (between 6x and 100x, most commonly 10x) and illumination, dermoscopy makes it possible to view structures in the epidermis and superficial dermis. This is made possible by the skin becoming translucent. As brought up in section 1.1.2, light is reflected when it reaches the skin surface. This can prevent the viewing of skin lesions and structures in the epidermis and dermis. To circumvent this and make a dermoscopic image visible, two things are needed in classical dermoscopy, using non-polarised light. The first requirement is the use of a liquid, to minimise the change in reflective index between the air and the skin. Different liquids have been used for this purpose including oils, alcohols, water, and gels. In a study where different liquids were compared, the authors found 70% ethanol to work best, resulting in few air bubbles, being odourless and evaporating quickly.[142] In certain conditions, such as on the nail bed or mucosa, as well as near the eyes ultrasound gel is sometimes preferred, as it will not sting and remains in place better.[143] The second requirement is contact between the device and the skin as flattening the skin surface also helps to decrease the reflecting/scattering of light. This is true for all devices using non-polarised light, i.e. non-polarised dermoscopy (NPD). The newer dermoscopes that use polarised light (polarised dermoscopy, PD) have another way of dealing with the above-mentioned problem. The polarised light, together with a polariser (a filter in front of the lens), blocks the reflected light, only allowing the light scattered from within the skin to reach the eye, resulting in a clear view of the lesion or structures without the need of immersion fluids or skin contact.[141]

It has become apparent that there are differences between NPD and PD. Although many visible structures appear basically the

same with the two methods, there are colours and structures that are more visible depending on the choice of dermoscope. PD appears better for viewing structures deeper in the dermis while NPD appears better for viewing the most superficial structures.[144] With new dermoscopes it is often possible to switch between the two forms of light, making it possible to get a good view of all relevant structures.

1.4.3 Colours and structures

When viewing skin lesions with dermoscopy, the structures and colours seen are a result of structures and chromophores in the skin. I.e. there are histopathological correlates that explain what is seen with the dermoscope.

The three main chromophores that are relevant in dermoscopy are melanin, haemoglobin, and keratin, each giving different colours when viewed with dermoscopy. The location of the chromophore in the skin further affects the colour. Melanin appears black in the stratum corneum, brown at the DEJ, grey in the papillary dermis and blue in the reticular dermis. Keratin can appear white, yellow, or orange and haemoglobin usually red to purple but congealed blood in the stratum corneum can also appear black. The colour white can also be caused by fibrosis in the dermis.[145, 146]

The dermoscopic pattern is also affected by the anatomy of the skin where the lesion is located, described in section 1.1.1. The common reticular pattern of CN on the body is caused by pigmentation at the DEJ, the lines caused correspond to pigmentation along the rete ridges, while the holes correspond to the dermal papillae *(figure 9a, and figure 1)*.[147, 148] In contrast, the most common pattern seen in facial lesions (i.e. the pseudonetwork) is caused by pigmentation along a flat DEJ interrupted by holes in the pattern related to the follicular openings *(figure 9b, and figure 2 left section)*.[8, 40] Finally, the parallel furrow pattern often seen in acral naevi is caused by pigmentation primarily at the DEJ beneath the crista profunda limitans *(figure 9c, and figure 2, right section)*.[9, 149]

Another common benign pattern in CN is grouped brown globules corresponding to nests of melanocytes located at the DEJ.[148]

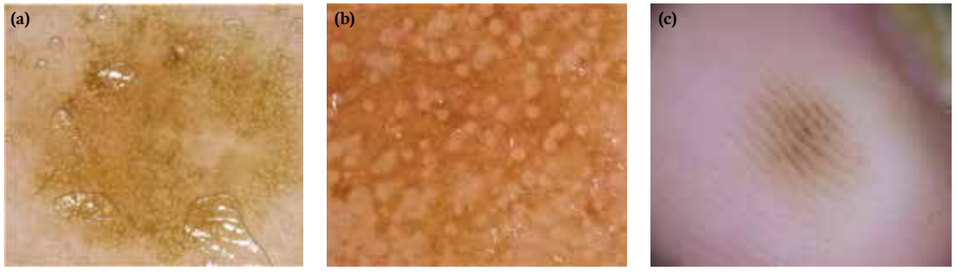


FIGURE 9. Dermoscopic patterns related to skin anatomy. (a) Reticular pattern found in junction naevi on the body, the network being a result of the pigmentation along the rete ridges. (b) Pseudonetwork on the face with brown homogenous pigmentation and holes due to follicular openings. (c) Parallel pattern in an acral naevus caused by melanocytes present at the crista profunda limitans. ***Photo:*** *Johan Dahlén Gyllencreutz (a-b) and John Paoli (c)*

This also applies to the dermoscopic features often seen in melanoma (listed in section 1.4.6), which are caused by melanocytes or melanin located in nests, single cells or in macrophages in different parts of the skin.[146, 148] The same is true for non-melanocytic lesions, such as SK, SL [150] or pigmented BCC.[151]

1.4.4 Effect on skin cancer diagnostics

Malignant melanoma

Numerous studies have been conducted showing the benefit of using dermoscopy for the diagnosis of melanoma, results that have been summarised in meta-analyses.[5, 152] In a later meta-analysis, including only studies in which dermoscopy was used in a clinical setting, Vestergaard et al. concluded that the sensitivity was 90% for dermoscopy compared to 72% for naked eye examination alone, a statistically significant difference (p=0.002). The specificity of dermoscopy was 90% while the naked eye reached 0.82, a difference that was not statistically significant (p=0.18). The relative diagnostic odds ratio (RDOR), a comparison taking both sensitivity and specificity into account, was 15.6 for dermoscopy over the naked eye, indicating a much greater diagnostic accuracy. When two small studies with extreme values for sensitivity were excluded, the RDOR was 9.0.[153]

In a retrospective study by Carli et al, there was an analysis of the impact of routine use of dermoscopy on the malignant/benign ratio, i.e. the number of benign lesions needed to be excised for every melanoma. For the dermatologists who started using dermoscopy, the malignant/benign ratio improved from 1:18 to 1:4.3 (p=0.037) while no improvement was seen for those that had not started using dermoscopy, 1:11.8 to 1:14.4. One conclusion they made was that the use of dermoscopy could lead to cost savings as well as reduce the workload of dermatological surgery.[7] In a later randomised controlled trial, Carli et al. found a significant reduction in patients referred for surgery in the group evaluated with dermoscopy as well as the naked eye, compared to only the naked eye: 9.0% compared to 15.6% (p=0.013).[154]

Non-pigmented skin tumours and non-melanoma skin cancer

Today, dermoscopy is used for the evaluation of all skin tumours but most studies designed to compare the use of dermoscopy to naked eye evaluation have been focused on melanoma of the common, pigmented type. Dermoscopy has also been tested for the diagnosis of hypo- and amelanotic melanoma, in a smaller number of studies. Pizzichetta et al. found a higher sensitivity and specificity for dermoscopy (96% and 88%, respectively) than without dermoscopy (89% and 65%, respectively) for the diagnosis of hypomelanotic melanoma. For truly amelanotic melanoma, dermoscopic diagnosis was found to be challenging.[155] Menzies et al. designed a simple model for the diagnosis of amelanotic melanoma with dermoscopy, however reaching only 70% sensitivity and 56% specificity. When changing the model to distinguish between malignant and benign lesions lacking significant pigment, the sensitivity was instead 96% but with a specificity of 36%.[156]

Studies have also been performed that focus on NMSC, usually focused on describing structures seen with dermoscopy in the different tumours, how often they are found and, sometimes, what sensitivity and specificity can be achieved. In a systematic review from 2007, Mogensen et al. describe dermoscopy of NMSC as being in its infancy. For BCC, they nevertheless describe sensitivity values from 87% to 96% and specificity values from 72% to 92%.[157]

In non-pigmented skin tumours, the vascular structures found are often important for differentiating between different malignant and benign lesions. Although there is no vascular structure completely specific for a single type of tumour, some structures are highly suggestive of one diagnosis or a limited number of diagnoses.[158] In two

reviews from 2010 focusing on diagnosing non-pigmented skin tumours, Zalaudek et al. describe vascular and other structures seen with dermoscopy in non-pigmented melanocytic and non-melanocytic skin tumours.[159, 160] Vessels seen with dermoscopy are described for a large number of lesions and combining vessel morphology, vessel arrangement and additional criteria, a diagnosis can be reached. The level of evidence is described as ranging from IIA (evidence from at least one controlled study without randomisation) to IV (evidence from expert committee reports or opinions or clinical experience of respected authorities or both). In a recently published, large study on non-pigmented skin cancer, Sinz et al. used expert, intermediate and novice dermoscopy users to study the accuracy of dermoscopy for non-pigmented skin cancers. They found that the use of dermoscopy significantly increased the possibility to differentiate malignant from benign as well as reaching a correct, malignant or benign diagnosis and making a correct management decision for malignant lesions. It was found that training in dermoscopy was needed to achieve many of the results.[161]

1.4.5 Training of dermatologists and PHC physicians

As stated above, the main benefits of dermoscopy has been proven for trained users only. In a study from 1995, trained users gained on average 10% on the sensitivity for melanoma, while those not trained lost on average 10% sensitivity.[162] In one study, it was shown that formal training in dermoscopy could increase the diagnostic accuracy by an average of 8.4% while 8 of 11 of those who did not receive training had a decreased sensitivity when dermoscopy was used.[163]

The use of web-based training of dermoscopy has also been studied, with results showing improvement in the diagnosis of melanoma when used by dermatologists not yet familiar with dermoscopy. The conclusion was that this type of "tele-education" was a suitable way of achieving improved skills in melanoma diagnostics.[164] Since then, the University of Graz, Austria have constructed a comprehensive online education program focusing on dermoscopy and skin cancer.[165] A clear benefit of this is making the education available to a much larger number of people.

Dermoscopy is most often used by dermatologists. However, in areas with a high occurrence of melanoma and NMSC, it could also be beneficial if other physicians acquired basic knowledge of this method, to better select appropriate patients in need of referral to dermatologists. In many countries, the group of physicians most suitable for an educational intervention are PHC physicians, both because they often see patients who seek health care for skin lesions of concern and because they see a lot of older patients with a higher risk of presenting with skin cancer.

There are two main studies on how dermoscopy training affects PHC physicians' ability to diagnose skin lesions. In 2000, Westerhoff et al. conducted a study randomising 74 PHC physicians to a short education in dermoscopy or to a control group without such education. The groups performed a pre-test and post-test with clinical and dermoscopic images of 50 melanomas and 50 naevi. No difference was found between the groups in the pre-test results, but in the post-test results, the group that had received education had an improved ability to differentiate melanoma from naevi, achieving a sensitivity of 75.9% for melanoma compared to 57.8% in the control group ($p<0.001$). No difference was seen in the specificity, i.e. the ability to correctly classify lesions as benign.[153] In 2006, Argenziano et al. conducted another study on PHC physicians that had been given a one-day training course on dermoscopy. They were randomised to use dermoscopy or naked eye evaluation for scoring skin lesions as benign or suggestive of skin cancer and in need of referral. The lesions were then re-evaluated by expert dermatologists. It was found that the dermoscopy users had a significantly higher sensitivity for skin cancer (including melanoma, SCC, and BCC), which was 79.2% compared to 54.1% in the control group ($p=0.002$). Meanwhile, there was no significant difference in specificity. Also, in the dermoscopy group, six malignant skin lesions were missed by the PHC physicians, compared to 23 in the naked eye group.[166]

1.4.6 Diagnostic algorithms

While the structures that become visible when using dermoscopy can of course be evaluated simultaneously to establish a diagnosis through simple pattern recognition, several algorithms have been developed, to aid in the diagnostic process and make the analysis more structured.

The two-step algorithm

When evaluating a skin lesion, it has been suggested that this should be done in two steps. In a first step, it is decided if the lesion is melanocytic or non-melanocytic and, in a second step, melanocytic lesions are judged to be benign or malignant. If no diagnosis can be made, excision should be considered.[167] For the second step, pattern analysis or a simplified algorithm can be used. Some simplified algorithms are also designed so that the first step should not be needed, the aim being to differentiate between benign and suspicious for malignancy and thereby selecting cases in need of referral or biopsy. Regardless of whether the initial focus is to differentiate between melanocytic and non-melanocytic or between benign and malignant, the first step describes relevant dermoscopic features and they will therefore be listed here, with additions made for types of lesions not initially included in the algorithms. *Figures 9-17* show many of the dermoscopic patterns and structures described in these algorithms.

Criteria for melanocytic lesions[145]

- Pigment network (can however also be found in some SL, SK, and in periphery of dermatofibroma)
- Pseudonetwork (on the face, can however also be found in non-melanocytic facial lesions)
- Aggregated brown or black globules (not multiple blue-grey globules)
- Branched streaks
- Homogeneous blue pigmentation (can also be found in some cherry angiomas, BCCs and in intradermal melanoma metastases)
- Parallel pattern (on palms/soles and mucosal areas)
- Blood vessels typical for melanocytic lesions (i.e. dotted vessels, comma-like vessels)

Apart from the histological classification of naevi (see section 1.2.1), it is also possible to classify naevi based on dermoscopy, into globular naevi, reticular naevi, starburst (Spitz/Reed) naevi, blue (homogenous) naevi, site-related naevi, naevi with special features, and unclassifiable melanocytic lesions.[168, 169]

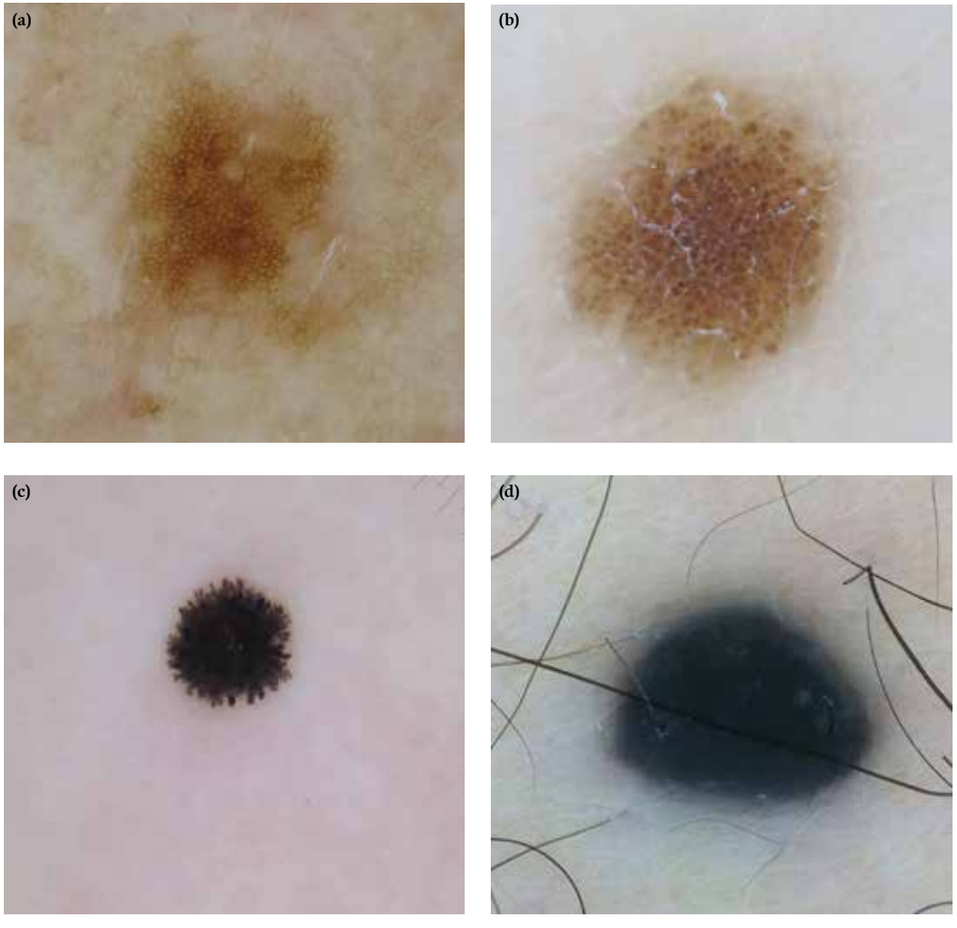


FIGURE 10. Dermoscopic features of melanocytic lesions. (a) Pigment network (reticular pattern) in a junction naevus. (b) Aggregated globules in a dermal naevus. (c) Symmetrically distributed branched streaks in a Reed naevus. (d) Homogeneous blue pigmentation in a blue naevus. ***Photo:*** *John Paoli*

Criteria for seborrhoeic keratosis[170]

- Multiple milia-like cysts
- Comedo-like openings (irregular crypts)
- Light-brown fingerprint-like structures
- Fissures/ridges (brain-like appearance)
- Hairpin vessels

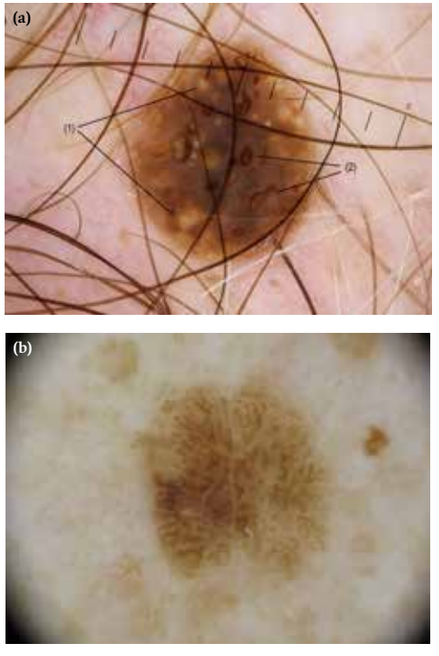


FIGURE 11. (a) Seborrhoeic keratosis (SK) with multiple milia-like cysts (1) and comedo-like openings (2). (b) SK with fissures and ridges, forming a "brain-like" appearance. ***Photo:*** *Johan Dahlén Gyllencreutz (a) and John Paoli (b)*

Criteria for basal cell carcinoma[171]
Absent pigment network AND one of the following:

- Arborising vessels
- Leaf-like areas
- Large blue-grey ovoid nests
- Multiple blue-grey globules
- Spoke wheel areas and concentric areas
- Ulceration (can also be seen in melanoma)
- Short linear or serpentine vessels
- Structureless white-red areas with multiple small ulcerations

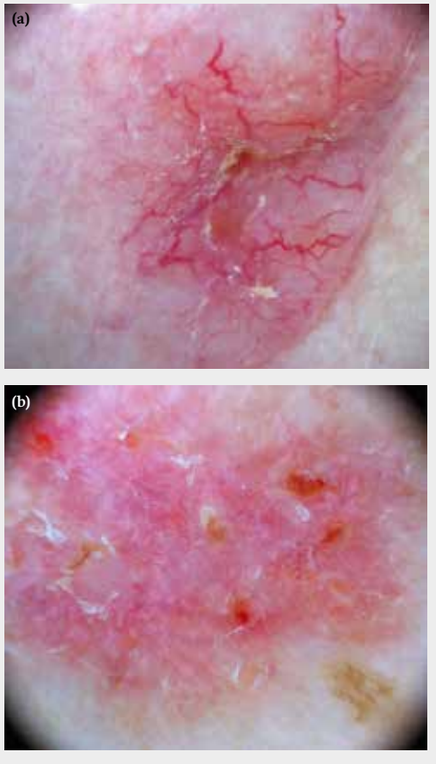
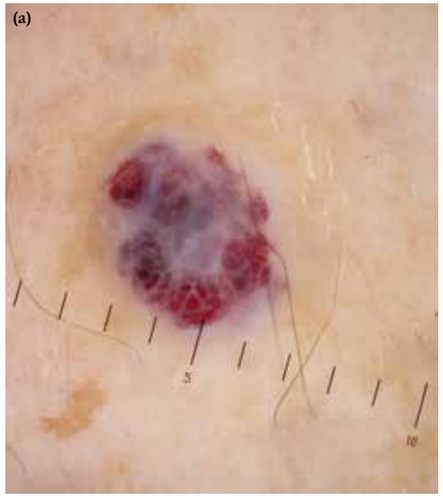


FIGURE 12. Dermoscopic view of basal cell carcinoma (BCC). (a) Nodular BCC with multiple arborising vessels. (b) Superficial BCC with short, linear or serpentine vessels and structureless white-red areas with multiple ulcerations. ***Photo:*** *Johan Dahlén Gyllencreutz*

Criteria for vascular lesions [145, 172]

- Red-blue lacunas
- Red-bluish to red-black homogenous areas



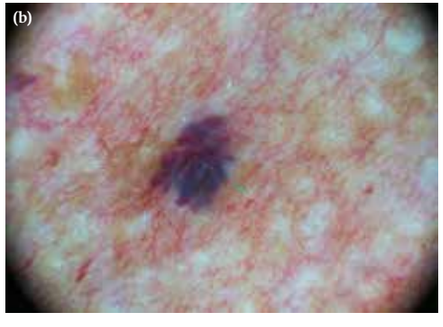


FIGURE 13. Two cherry angiomas showing red-blue lacunas (a) and red-bluish, homogeneous areas (b).
Photo: *Johan Dahlén Gyllencreutz*

Criteria for pyogenic granuloma [173]

- Reddish homogenous areas
- White collarette
- White intersecting or rail lines
- Polymorphous vessels
- Ulceration

Since no criteria exist that can completely differentiate pyogenic granuloma from amelanotic/hypomelanotic melanoma, it is recommended that these lesions are excised and analysed histopathologically.

Criteria for dermatofibroma [174]

- Central white scar-like patch
- Delicate peripheral pigment network

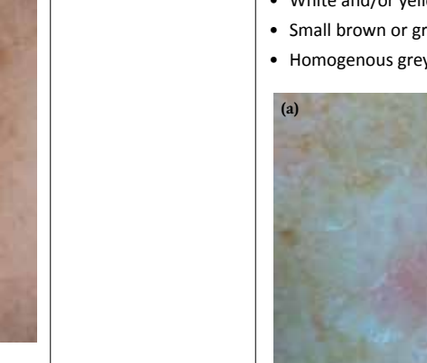


FIGURE 14. Two dermatofibromas showing a central scar-like patch and peripheral pigmentation.
Photo: *Johan Dahlén Gyllencreutz*

Criteria for squamous cell carcinoma [159, 175]

- White circles
- Keratin mass (located at the centre of the lesion in keratoacanthoma and well-differentiated SCC)
- Blood spots/ulceration
- Structureless white areas
- Polymorphous vessels (peripheral hairpin vessels in keratoacanthoma and well-differentiated SCC)

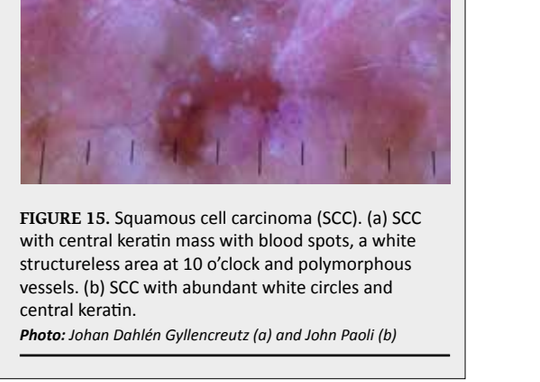


FIGURE 15. Squamous cell carcinoma (SCC). (a) SCC with central keratin mass with blood spots, a white structureless area at 10 o'clock and polymorphous vessels. (b) SCC with abundant white circles and central keratin.
Photo: *Johan Dahlén Gyllencreutz (a) and John Paoli (b)*

Criteria for SCC in situ /Bowen's disease [176, 177]

- Glomerular vessels
- White and/or yellow scales on surface
- Small brown or grey dots/globules, sometimes in linear or patchy arrangement (in pigmented SCC in situ)
- Homogenous grey to brown pigmentation (in pigmented SCC in situ)

FIGURE 16. Two cases of squamous cell carcinoma in situ with glomerular vessels and white scales.
Photo: *Johan Dahlén Gyllencreutz (a) and John Paoli (b)*

Criteria for actinic keratosis [178]

- Erythema or red pseudonetwork
- White and/or yellow keratin plugs in the hair follicles
  Together these structures may form a strawberry-like pattern
- White and/or yellow surface scales
- Rosettes (four white dots within a hair follicle, seen only with PD)

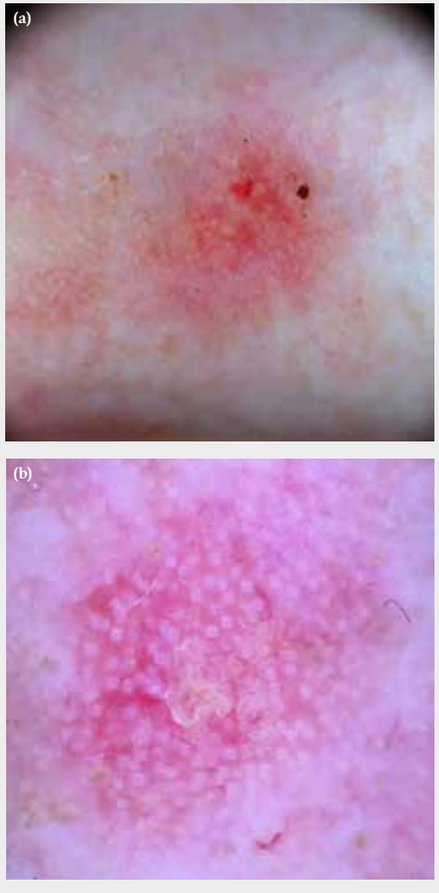


FIGURE 17. (a) Actinic keratosis (AK) with erythema and white-yellow follicular openings, forming a "strawberry-like" pattern. (b) AK with visible rosettes and scales. ***Photo:*** *Johan Dahlén Gyllencreutz (a) and John Paoli (b)*

While most of the structures listed can be seen equally well regardless of what type of dermoscope is used, some structures are seen more clearly with one type of light. Some of the noted differences are that NPD is better for viewing some blue-grey structures as well as milia-like cysts and comedo-like openings found in SKs, while PD is better for the viewing of vessels (because of lack of pressure).[144] More recently new relevant structures have been discovered, visible only with PD, including white shiny lines and rosettes.[179, 180]

Pattern analysis

Pattern analysis, the original method for using dermoscopy to distinguish between a benign and a malignant pigmented skin lesion (PSL), was described in 1987 by Pehamberger et al.[145] Dermoscopy parameters and patterns were described and these structures are still used, together with some additions. The method of pattern analysis has since then been revised by the International Dermoscopy Society (IDS), including additions regarding site-specific features.[181, 182] Global patterns, local features and site-related features are presented in *tables 3-5*.

TABLE 3. Modified pattern analysis, global pattern.

Dermoscopic pattern	Definition	Diagnostic significance
Reticular	Pigment network covering most of the lesion	Melanocytic lesion
Globular	Numerous, variously sized, round to oval structures with various shades of brown or black	Melanocytic lesion
Cobblestone	Large, closely aggregated, somewhat angulated globule-like structures resembling a cobblestone road	Dermal naevus
Homogenous	Diffuse, brown, grey-blue, or grey-black pigmentation in the absence of other distinctive local features	Melanocytic (blue) naevus
Starburst	Pigmented streaks in a radial arrangement at the edge of the lesion	Spitz/Reed naevus
Parallel	Pigmentation on palms/soles that follow the furrows or ridges of acral skin, occasionally arranged at right angles to these structures	Acral naevus/ melanoma
Multicomponent	Combination of three or more of the above patterns with asymmetric distribution	Melanoma
Non-specific	Pigmented lesions lacking the above patterns	Possible melanoma or non-melanocytic lesion

TABLE 4. Modified pattern analysis, local features.

Dermoscopic feature	Definition	Diagnostic significance
Pigment network	Typical pigment network: light- to dark-brown network with small, uniformly spaced network holes and thin network lines distributed more or less regularly throughout the lesion and usually thinning out at the periphery.	Benign melanocytic lesion (figure 9a and 10a)
	Atypical pigment network: black, brown, or grey network with irregular holes and thick lines, often wider than the holes	Melanoma (figure 18b)
Dots/globules	Black, brown, round to oval, variously sized structures regularly or irregularly distributed within the lesion	If regular, benign melanocytic lesion (figure 10b) If irregular, melanoma (figure 18a)
Streaks (previously described separately as pseudopods and radial streaming)	Bulbous and often kinked or finger-like projections seen at the edge of a lesion. They may arise from network structures but more commonly do not. They range in colour from tan to black.	If regular, benign melanocytic lesion (Spitz/Reed naevus) (figure 10c) If irregular, melanoma (figure 18b)
Blue-white veil	Irregular, structureless area of confluent blue pigmentation with an overlying "ground-glass" film. The pigmentation cannot occupy the entire lesion and usually corresponds to a clinically elevated part of the lesion	Melanoma (figure 18a)
Regression structures	White scar-like depigmentation and/or blue-grey pepper-like granules usually corresponding to a clinically flat part of the lesion	Melanoma
Hypopigmentation	Areas with less pigmentation than the overall pigmentation of the lesion	Non-specific
Blotches	Black, brown, and/or grey structureless areas with symmetrical or asymmetrical distribution within the lesion.	If symmetrical; benign melanocytic lesion If asymmetrical; melanoma
Vascular structures	Comma-like vessels Hairpin vessels	Dermal naevus Seborrheic keratosis or SCC/keratoacanthoma.
	Dotted vessels	Melanocytic lesion (if irregular, melanoma)
	Glomerular vessels Linear irregular vessels	Bowen's disease Melanoma
	Vessels and/or erythema within regression structures	Melanoma

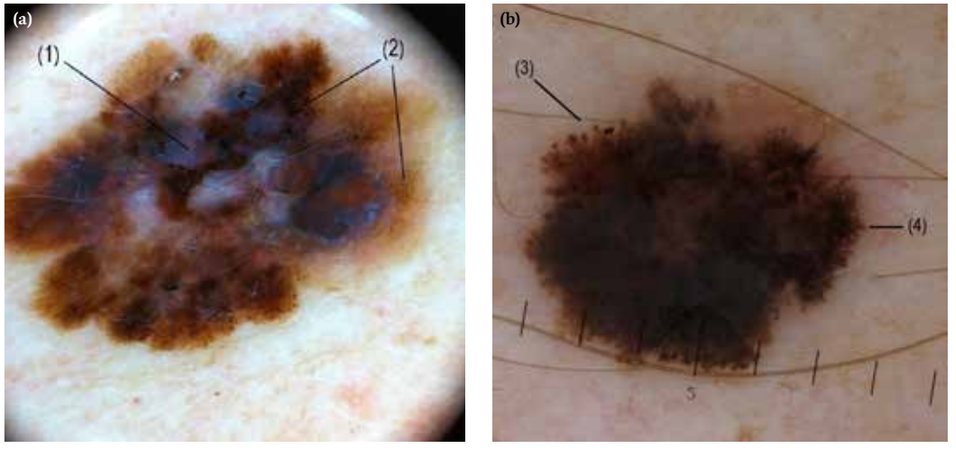


FIGURE 18. (a) Melanoma showing blue-white veil (1), asymmetric dots and globules (2) and multiple colours. (b) Melanoma showing atypical pigment network (3) and streaks (4). ***Photo:*** *Johan Dahlén Gyllencreutz*

TABLE 5. Modified pattern analysis, site-related features [8, 9]

Diagnostic features	Definition	Diagnostic significance
Face: ***Typical pseudonetwork***	Brown pigmentation with round, equally sized network holes corresponding to the pre-existing follicular ostia	Benign lesion, including CN and SL (figure 9b)
Annular-granular structures	Multiple blue-grey dots surrounding the follicular ostia with an annular-granular appearance	Melanoma (figure 19a)
Grey pseudonetwork	Grey pigmentation surrounding the follicular ostia, formed by the confluence of annular-granular structures	Melanoma
Asymmetrically pigmented follicles	Asymmetric annular pigmentation around follicular ostia	Melanoma (figure 19a)
Rhomboidal structures	Grey-brown pigmented lines surrounding the follicular ostia with a rhomboidal or zig-zag appearance	Melanoma (figure 19a)
Palms/soles: ***Parallel furrow pattern***	Pigmentation following the furrows of acral skin	Acral naevus (figure 9c)
Lattice-like pattern	Pigmentation following and crossing the furrows of acral skin	Acral naevus
Fibrillar pattern	Numerous, finely pigmented filaments perpendicular to the furrows and ridges of acral skin	Acral naevus
Parallel ridge pattern	Pigmentation following the ridges of acral skin	Melanoma (figure 19b)

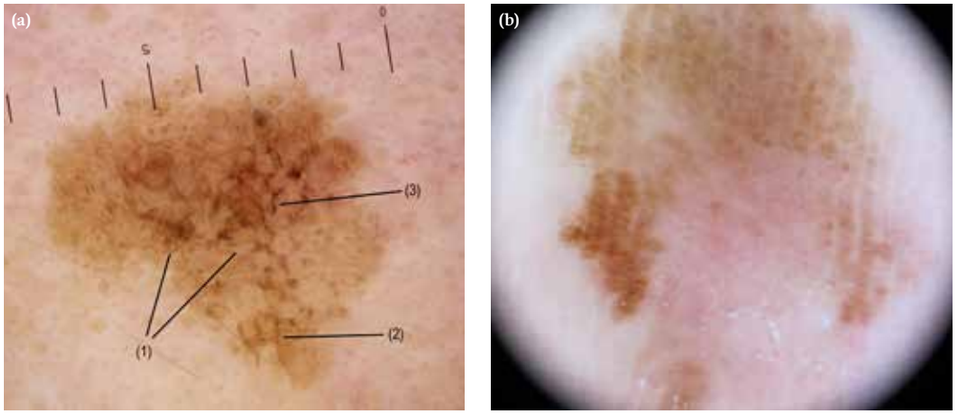


FIGURE 19. (a) Lentigo maligna with asymmetrically pigmented follicles (1), annular-granular structures (2), and some early rhomboidal structures (3). (b) Acral melanoma showing parallel ridge pattern as well as an area with depigmentation.
Photo: *Johan Dahlén Gyllencreutz (a) and John Paoli (b)*

Algorithms for the diagnosis of melanoma by dermatologists

Most of the early simplified algorithms were designed primarily to differentiate melanoma from naevi. They can be used in the second step of the two-step algorithm, as an alternative to pattern analysis. Although meant to be easier to use than pattern analysis for non-experts in dermoscopy, they were not specifically designed to be used by other physicians such as those working in PHC. A study by the IDS, using Fleiss kappa (κ) to measure agreement between many dermoscopists, found fair to good interobserver agreement and good to excellent intraobserver agreement for pattern analysis and the three first algorithms listed below. Pattern analysis resulted in the best diagnostic performance, while the simplified algorithms had comparable sensitivity but lower specificity.[167]

The ABCD rule of dermatoscopy

This was the first simplified algorithm for diagnosing melanoma, presented by Stolz et al. in 1994.[183, 184] This method is based on scoring asymmetry, border, colour and dermoscopic structures and calculating a total score *(table 6)*.

TABLE 6. The ABCD rule of dermoscopy.

Criterion	Description	Score	Weight factor
Asymmetry	In 0, 1 or 2 perpendicular axes; assess not only contour, but also colours and structures	0-2	X 1.3
Border	Abrupt ending of pigment pattern at the periphery in 0-8 segments	0-8	X 0.1
Colour	Presence of up to 6 colours (white, red, light brown, dark brown, blue-grey, black)	1-6	X 0.5
Dermoscopic structures	Presence of pigment network or structureless homogeneous areas, branched streaks, dots, and globules	1-5	X 0.5

Formula: (A x 1.3) + (B x 0.1) + (C x 0.5) + (D x 0.5). Score: < 4.75 benign; 4.8-5-45 suspicious; > 5,45 Malignant.

Menzies' Method

This algorithm was introduced by Menzies et al. in 1996.[185] It is based on first evaluating the presence of negative features that rule out melanoma and then, if negative features are missing, looking for positive features that are clues to melanoma. For the diagnosis of melanoma, a lesion must have neither of the two negative features and at least one positive feature. There are no calculations performed in this algorithm.

Negative features

- Symmetry of pattern
- Presence of a single colour

Positive features

- Blue-white veil
- Multiple brown dots
- Pseudopods
- Radial streaming
- Scar-like depigmentation
- Peripheral black dots/globules
- Multiple (5-6) colours
- Multiple blue/grey dots
- Broadened network

The 7-point checklist

This algorithm was introduced by Argenziano et al. in 1998 and is meant to simplify the classic pattern analysis by scoring a lesion using 7 criteria (3 major and 4 minor).[186]

Major criteria	Score
• Atypical pigment network	2
• Blue-whitish veil	2
• Atypical vascular pattern	2
Minor criteria	
• Irregular streaks	1
• Irregular pigmentation	1
• Irregular dots/globules	1
• Regression structures	1

A score of less than 3 indicate non-melanoma while 3 or more indicates melanoma. In 2010, a new way of using the algorithm was introduced. In this revised version, the seven criteria are unchanged, but not divided into major and minor criteria. In the revised 7-point checklist, only one positive criterion is needed to recommend excision.[187]

CASH-algorithm

An algorithm developed in 2007 by Henning et al. that also takes into account the evaluation of architectural disorder when scoring lesions. There are 4 criteria that are scored *(table 7)*. A score of over 8 should cause suspicion of melanoma.[188]

TABLE 7. The CASH-algorithm

Criterion	Score	Sum (2-17)
Colour (C)	1 point for each: light brown, dark brown, black, red, white, blue	1-6
Architectural disorder (A)	0 points = none/mild 1 point = moderate 2 points = marked	0-2
Symmetry (S)	0 points = biaxial symmetry 1 point = monoaxial symmetry 2 points = biaxial asymmetry	0-2
Homogeneity/heterogeneity based on the number of dermoscopic structures (H)	1 point for each: network, dots-globules, streaks-pseudopods, blue-white veil, regression, blotches, polymorphous vessels	1-7

Algorithms also meant to be used by non-dermatologists

Some simplified algorithms have been designed with the intention to not only help non-experts in dermoscopy to correctly manage skin lesions but also to help non-dermatologists single out lesions that need to be referred to dermatologists.

3-point checklist

This algorithm was introduced in 2003 by Soyer et al. with the intention to be used by non-dermatologists as a screening method primarily for melanoma, to select lesions to refer to dermatologists.[189] There are only three criteria to evaluate, each giving a score of one. As two of the three criteria are relevant also in NMSC it is considered as a screening tool for that as well. A score of 2 or more should be interpreted as suspicious.

Criteria	Score
1. Asymmetry (in colours and structures)	1
2. Atypical pigment network	1
3. Blue-white structures (any blue or white colour)	1

Chaos and clues

This algorithm designed by Kittler et al. and evaluated in a study by Rosendahl et al. is meant to be used for all skin lesions of concern and aims at differentiating those lesions that need biopsy or referral to a dermatologist/expert rather than give a specific diagnosis.[190, 191] It involves first looking for the presence of chaos in colour or structure and, if that is found, searching for any of the 8 clues to malignancy *(see list below)*. Finding chaos and one clue is required to suspect malignancy and no calculations are made.

Chaos *– defined as asymmetry produced by the pattern of dermoscopic colours or structures within a lesion. The symmetry of shape is not evaluated.*

Clues:

1. Eccentric structureless area (displaying any colour other than skin colour)
2. Thick reticular or branched lines
3. Grey or blue structures (including dots, lines, circles, or clods)
4. Peripheral black dots or clods
5. Segmental radial lines or pseudopods
6. Polymorphous vessels
7. White lines
8. Parallel ridge patterns in acral skin

If pattern analysis can be applied to securely reach the diagnosis of SK the specificity of this algorithm is increased. Knowing the dermoscopic pattern of common, benign lesions can in this way help in diagnosing the malignant lesions.

The Triage Amalgamated Dermoscopic Algorithm (TADA)

This recent algorithm introduced by Rogers et al. in 2016 also uses knowledge about common, benign lesions to form the basis of selecting lesions for biopsy or referral.[192] It is meant to be used by PHC physicians among others. This algorithm uses a stepwise procedure to evaluate both pigmented and non-pigmented lesions. If the structures listed in any of the steps are found, the proper action is taken. If not, the next step is evaluated.

If none of the structures in the different steps are found the recommendation is that the patient continue to self-monitor the lesions and react to any changes or new symptoms.

Finding	Action
Step 1 Unequivocal:	**Reassure**
• Angioma	
• Dermatofibroma	
• Seborrheic keratosis	
Step 2 Either of these patterns:	**Biopsy/refer**
• Architecturally disordered	
• Starburst	
Step 3 Any of these features:	**Biopsy/refer**
• Blue-black or grey colour	
• White structures	
• Negative network	
• Ulcer/erosion	

1.4.7 The diagnostic process

The proper way of using dermoscopy is to evaluate most lesions rather than to use naked eye evaluation of the whole body and then only use dermoscopy of clinically suspicious lesions. One potential reason not to use dermoscopy in this way is a perceived lack of time. However, in a study by Zalaudek at al., it was concluded that a skin evaluation using only the naked eye takes approximately 70 seconds while the use of dermoscopy for a TBSE takes approximately 140 seconds.[193] The fact that three minutes would be enough for a proper skin examination removes any real reason not to use dermoscopy in the correct way.

In 2005, Gachon et al. described principles used by dermatologists for differentiating naevi from melanoma in clinical practice.[194] The three major steps described as being most important are:

- **A cognitive process** – Assessment of the overall pattern of the lesion of concern.
- **A comparative process** – The "ugly duckling sign" comparing the lesion of concern with the other naevi of that specific patient.
- **An interactive process** – Knowledge of recent change in the lesion of concern.

For patients with multiple naevi *(figure 20)*, comparing the skin lesions of a given patient with each other has proven to be an important part of a skin evaluation, making it possible to reduce the number of excisions greatly compared to what is achieved by just analysing the pattern of an individual lesion.[195]

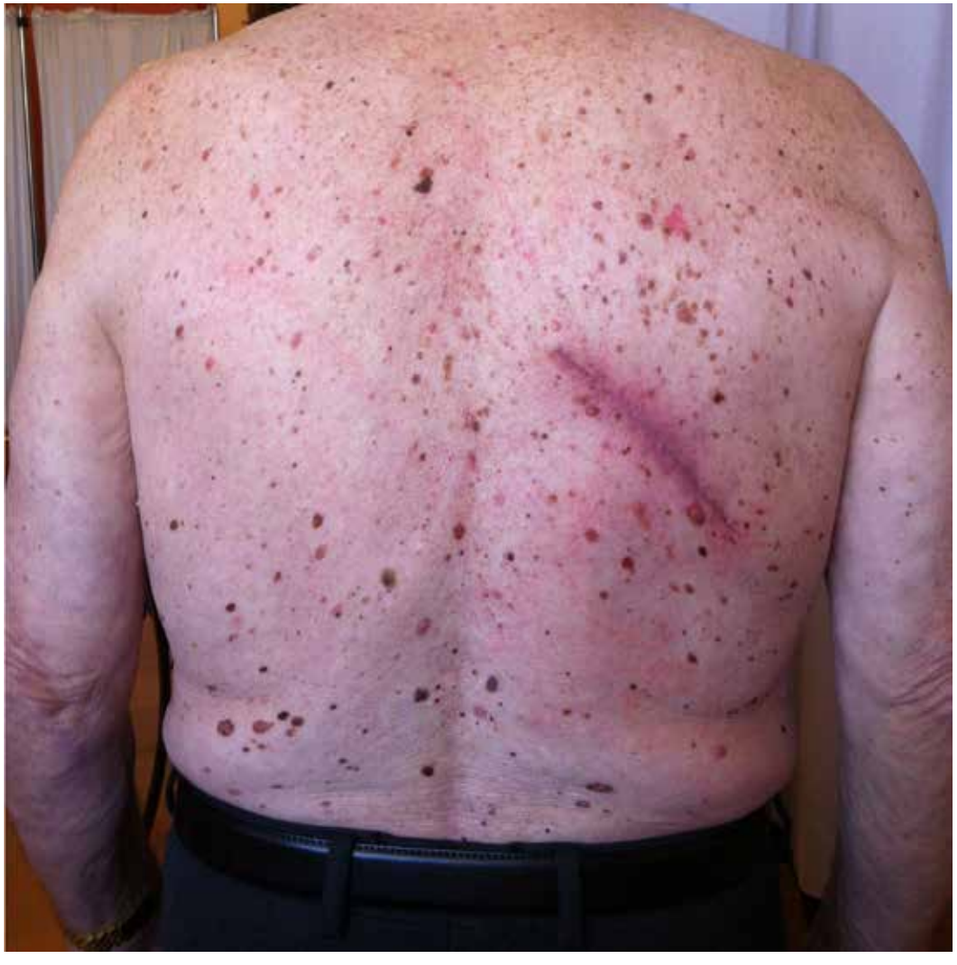


FIGURE 20. A patient with a previous melanoma and a large number of naevi/AMLs. The cognitive, comparative, and interactive processes described above are needed to correctly detect melanoma. ***Photo:*** *John Paoli*

Apart from this, it is important to consider other patient-related aspects. In young patients, it is perfectly normal to acquire new naevi, or have growing naevi, something that should be considered suspicious in older patients.[196, 197] The colour and pattern of an individual's naevi can also be related to pigmentary traits, with lighter skin often having light brown or pinkish-red naevi while darker skin can contain darker naevi.[198] Thus, a naevus pattern that is normal in one individual can be suspicious in another, something that is relevant to consider when discussing digital dermoscopy (DD) and teledermoscopy.

1.4.8 Digital dermoscopy

Dermoscopic images have been used for many years. In fact, in two earlier meta-analyses on the effect of dermoscopy for the diagnosis of melanoma, many of the studies included were conducted using images rather than based on the direct evaluation of patients.[5, 152] Digital dermoscopic images have also been found to have specific uses. One common use of DD is to follow equivocal or atypical lesions over time. This is mostly used to follow AMLs where it is not possible to clearly establish a diagnosis of naevus or melanoma at the initial evaluation. In this situation, lesion(s) can be photographed with a DD device and the patient can come back to the dermatology department after a given time to photograph the lesion(s) again. If enough change is seen, this is interpreted as a sign of malignancy and the lesion is excised. The optimal interval between visits for this type of short-term DD monitoring has been described as 3 to 4.5 months, as this will make it possible to detect most melanomas.[199] However, a category of slow-growing melanomas has been described, and for those lesions longer follow-up may be needed as change might not be seen in a short time interval.[200]

For patients with multiple AMLs, DD can be used by itself or in combination with total body photography (TBP), where the device used to photograph individual lesions is also used to acquire standardised images of the entire body and help identify new or changing lesions. A combination of the two methods may be best for high-risk patients, as it has shown to make it possible to detect melanoma early while keeping the number of unnecessary excisions of benign lesions low.[201, 202] It has been shown that patients with familial melanoma as well as those with a large number of clinically AMLs benefit the most.[186] In different studies, melanoma has made up between 0-22.2% of excised lesions, between 0-2% of monitored lesions and the proportion of monitored patients that developed melanoma has been between 0-10%.[203]

Benefits and risks with digital dermoscopy

A study of the benefits and risks with this type of digital follow-up has been published by Kittler and Binder. By comparing how dermatologists chose to manage melanocytic lesions, depending on the possibility of follow-up, it was found that having this option can decrease the sensitivity for melanoma at the first visit, while increasing the specificity. At the second visit, diagnostic accuracy for melanoma is increased, with higher sensitivity for all dermatologists participating in the study. The specificity however, was increased only for those with experience with the method. For this method of follow-up to work properly, patients must also be compliant with follow-up visits.[204] If a patient with equivocal melanocytic lesions doesn't show up for the digital follow-up, there is a risk that a melanoma is not excised *(figure 21)*. One study reported compliance levels of only 46%[205] while another found that compliance varied depending on the time to the first follow-up visit, being 84% at three months, 63% at six months and 30% at twelve months.[203]

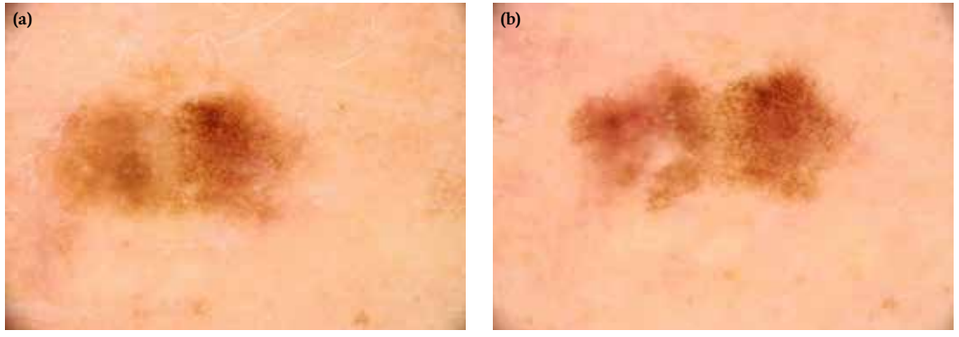


FIGURE 21. Images from a patient with multiple atypical melanocytic lesions that were planned to be monitored with digital dermoscopy, but where the patient did not attend the follow-up visit. (a) Lesion photographed in November 2012, showing a similar pattern as other lesions being photographed. (b) The same lesion photographed in March 2015, when the patient returned because of concern for another lesion. The left part of the lesion had changed and, after excision, histopathology confirmed early melanoma. ***Photo:*** *Johan Dahlén Gyllencreutz*

Carli et al. found that using digital follow-up resulted in a number of initial melanomas left unexcised until the second consultation,[154] indicating the importance of carefully selecting the lesions followed this way. The cases which proved to be melanoma in the study included a melanoma in situ and a thin melanoma with a Breslow depth of 0.4 mm. Thus, the patients were not put at risk by the delayed excisions. However, one potential risk with DD for the follow-up of AMLs is that the method could delay the biopsy or treatment of aggressive cancers. Because of this, digital follow-up is contraindicated for nodular or raised lesions.[206]

1.5 Other diagnostic methods

While dermoscopy has become the most common non-invasive method to evaluate skin lesions, other methods have also been developed, that can complement dermoscopy or have specific uses in the management of skin cancer.

1.5.1 Imaging-based methods

There are several methods that can present the user with an image of a skin lesion. Like dermoscopy, a level of expertise is needed to interpret the acquired images. With these methods there is a trade-off between the resolution of the image and how deep into the skin it is possible to see. The methods with high resolution do not visualise deeper parts of the skin and the ones that make it possible to see deeper structures have lower resolution. Examples of such methods are listed here:

- In vivo reflectance confocal microscopy uses a laser with a wavelength of 830 nm to form a horizontal view of the epidermis and papillary dermis, similar to a horizontal histopathological slide, down to a depth of 0.2-0.3 mm. It has been found to have sensitivity at the same level as dermoscopy.[207, 208]
- Multiphoton laser scanning microscopy also uses a laser with a wavelength of 780 nm to give a horizontal view of the epidermis and superficial dermis, down to 0.13 mm. Potential uses include the non-invasive diagnosis of superficial skin cancer.[209]
- Optical coherence tomography uses light with a wavelength of 1300 nm to form a vertical view of the skin, down to 1-2 mm depth. Potential uses include determining the tumour thickness preoperatively.[210]
- High-resolution ultrasound can also be used to achieve a vertical view of the skin down to 7-8 mm depth. This has also been evaluated to measure tumour thickness.[211]

1.5.2 Automatic detection without imaging

There are also methods meant to automatically detect melanoma and other skin cancers. Looking specifically at melanoma, a few examples will be presented here. Generally, a very high sensitivity can be achieved but with a low specificity.

- Computer-aided multispectral digital analysis (MelaFind®) involves the creation of digital multispectral images using ten different spectral bands, followed by automatic image analysis (sensitivity 98.4% and specificity 9.9%).[212]
- Electrical impedance spectroscopy (Nevisense®) measures the impedance (i.e. the resistance to alternating current) in skin lesions, which is different in naevi and melanoma (sensitivity 96.6% and specificity 34.4%).[213]
- Real-time Raman spectroscopy, which uses a diode laser at 785 nm and measures reflected light with varying vibration signals from different molecules. If sensitivity is set to 95%, the specificity is 38%.[214]

1.5.3 Automatic detection based on images

This type of automated diagnostic system uses the ever-increasing power of modern computers to detect signs of malignancy in clinical or dermoscopic images. In a meta-analysis from 2009, it was found that the pooled sensitivity for melanoma was non-significantly higher for the automated systems compared to dermoscopy (91% vs 88%, p=0.076) while specificity was significantly lower with the automated system (79% vs 86%, p<0.001). There was no significant difference in diagnostic odds ratio, (DOR 57.8 vs 51.1, p=0.783).[215]

In a more recent study, that has received a lot of attention, Esteva et al. used a deep convolutional neural network with a deep learning algorithm, based on 129,450 images including 3,374 dermoscopic images, to diagnose skin lesions including melanoma. They found that the automated system matched the performance of 21 dermatologists regarding NMSC classification, melanoma classification and melanoma classification using dermoscopy.[216]

Most studies on this type of diagnostic method are not conducted under real-life conditions, usually being based on images of previously diagnosed cases rather than on patients evaluated prospectively. In contrast, a prospective clinical trial was conducted in 2009, evaluating the feasibility of an automated, neural network based diagnostic system. The system was used by physicians without training in dermoscopy and the outcome was compared with that of expert dermatologists using dermoscopy. It was found that the automated system had a lower sensitivity for melanoma (72% vs 96%, p=0.001) but a higher specificity (82% vs 72%, p<0.0001). Three melanomas were missed by the automated system because the users did not select them for examination.[217] Thus, this type of system does not appear to remove the need for skill in dermoscopy. It is also interesting to see the difference in the results, depending on how the studies are designed.

1.6 Telemedicine

Telemedicine (e-health) is defined as when communication technologies are used in healthcare for the exchange of medical information over a distance. It can be used for such areas as diagnosis, treatment, research, and education. The term was first used in 1970[218, 219] but there are earlier reports of methods that should be considered telemedicine. In the first decade of the 1900s, Wilhelm Einthoven, the inventor of the electrocardiogram, also used a "telecardiogram" to transmit electrocardiograms via the telephone network.[220] During the 1950s through to the 1970s, various telemedicine projects were conducted in the USA, ranging

from distance interviewing of psychiatric patients to monitoring physiological parameters of astronauts while in outer space.[221] It was during the 1990s that the use of telemedicine really started to increase, related to the rapid advancement of information and telecommunication technologies and digital data transmission. A variant of telemedicine, mobile telemedicine, is when the equipment used to transfer medical data over a distance is mobile rather than stationary. This has become feasible with the development of more advanced mobile phones and other devices.

1.7 Teledermatology

Because of the visual nature of dermatological conditions, it is logical that telemedicine has been used in this specialty. The first trial of viewing dermatological conditions at a distance was conducted in 1972, at Massachusetts General Hospital. Dermatologists viewed slides of dermatological lesions directly as well as on a television screen and were often able to reach the same diagnosis.[222] Apart from that, examples of articles about the use of telemedicine for dermatological evaluations, i.e. teledermatology (TD), were published in the mid-1990s. In 1995, Peredina and Brown described a TD research program in a rural area of Oregon, USA that had a shortage of dermatologists.[223] Meanwhile, in 1996, Jones et al. conducted a pilot study on TD in Scotland finding that the correct diagnosis was established this way for most of the 51 patients included, and that over half could be managed through this medium alone.[224] In 1997, one of the first studies comparing telediagnosis with face-to-face (FTF) diagnosis was conducted by Zelickson and Homan, with patients recruited from a nursing home. They found the telediagnosis to be correct in 88% of evaluations and the treatment plan to be correct in 90% of evaluations.[225] In 2002, a randomised controlled trial on TD was published by Whited et al. They found that, compared to a text-based electronic referral, TD resulted in significantly shorter waiting times (median 42 vs 127 days, p=0.0001) and more preventable visits (18.5% vs 0%, p<0.001).[226] Since then, the number of uses and publications of TD has increased greatly.

Mobile TD is a logical evolution of TD, as mobile phones and other mobile devices now have digital cameras and connection to the internet. An early example of mobile TD was a study by Braun et al. in 2005, comparing the FTF evaluation of leg ulcers with distance evaluation based on digital images acquired by mobile phone. They found the diagnostic concordance to be very high, with Cohen's kappa (κ) scores of up to 0.94, representing almost perfect concordance.[227] Other early studies were conducted by the TD research unit in Graz, Austria. Using the cameras of first generation mobile phones and personal digital assistants (PDAs), a comparison was made between the telediagnosis and the FTF diagnosis. The average diagnostic concordance was 70% with mobile phones and 80% with PDAs.[228, 229] The low image resolution of the cameras integrated into the first generations of mobile phones and other devices limited the use of mobile TD, but as the cameras have gotten better, this is no longer the case. In a more recent study, Nami et al. compared smartphone-based mobile TD with FTF visits, finding high levels of agreement for diagnosis (91%, Cohens κ=0.906) and therapy (80%, κ=0.701). The agreement for skin tumours was at the same level as all diagnoses combined (91%), despite the lack of dermoscopic images. However, two malignant skin tumours were diagnosed as benign by TD and one conclusion was that dermoscopy is mandatory for TD used on skin tumours.[230]

In 2011, a systematic review was published, including 78 TD studies published between 1990 and 2009. The main conclusion was that the diagnostic accuracy of TD was inferior to, but acceptable compared to that of FTF visits, e.g. the weighted mean absolute difference for primary diagnostic accuracy for pigmented skin lesions was 5% better for FTF than with TD. It was also found that time to treatment was shorter with TD and that the number of FTF visits could be decreased with TD. For some outcomes, the evidence was considered too limited to reach any conclusions, including the impact on clinical outcomes and management as well as cost analysis.[231]

Thus, there are limited data on how the use of TD affects the costs related to skin cancer. Some studies comparing costs of TD referral with a traditional referral system report significant savings[232, 233] while others report savings to be dependent on large travel distance to a dermatologist or substantial number of avoidable FTF visits.[234]

A systematic review focused on symptomatic cancer was performed in Sweden in 2013, by the Swedish Council on Health Technology Assessment (Statens beredning för medicinsk och social utvärdering; SBU). One of the main conclusions was that the use of photographs in skin tumour referrals between PHC and dermatologists (i.e. TD) can shorten the time to treatment.[235]

1.8 Teledermoscopy

When dermoscopic images are included in a TD consultation it is referred to as teledermoscopy (TDS) a method used primarily for the evaluation of skin lesions with a suspicion of malignancy. The above-mentioned review from 2011 found TDS to improve accuracy rates up to 15% over TD.[231] Later studies have confirmed that compared to TD, TDS can provide improved sensitivity and specificity and make it possible to make correct management decisions regarding skin lesions more often.[236]

The first studies on TDS were published in the late 1990s. In 1998, Provost et al. sent compressed dermoscopic images of AMLs and melanomas over the internet, finding that this method was feasible for diagnosing skin tumours, comparable to viewing regular photographs.[237] Other early studies were published by Piccolo et al. in 1999 and 2000, reporting diagnostic concordance with FTF of 91% in the first study and in the second finding 77-95% agreement between telediagnosis and histopathology compared to 91% agreement between FTF diagnosis and histopathology.[238, 239] More recent studies show similar results. In a study published in 2008, May et al. found TDS to improve triaging and reduce waiting times for patients with skin cancer compared to a conventional referral system without images. Regarding melanoma, all but one patient (who failed to attend the first booked visit) in the TDS group was treated within the stated maximum waiting time of 62 days, compared to 68% in the group referred without images.[240] Tan et al. later studied TDS as a triaging tool for patients referred to a skin lesion clinic. They found agreement between TDS and FTF diagnosis in 88% of lesions and, compared with histopathology, the sensitivity for melanoma and SCC was 100%. Although 10.5-13.8% of cases were considered as having a clinically significant difference between TDS and FTF diagnoses (benign in TDS and malignant in FTF) there was only one malignant case missed with TDS (a BCC diagnosed as an AK), meaning that in several individual cases, TDS was superior to FTF diagnosis.[241]

While the above-mentioned studies show similar, promising results, there are also studies with more mixed results. Warshaw et al. have published two studies, on pigmented and non-pigmented neoplasms. For non-pigmented lesions, TD/TDS was found to be inferior to FTF regarding diagnostic accuracy (when compared to histopathology) but equivalent regarding management plan.[242] For pigmented lesions, TD/TDS was also found to be inferior to FTF regarding diagnostic accuracy while TD/TDS was equivalent or superior to FTF for the management plan. However, they concluded that 3 to 5 of 36 melanomas would be mismanaged with TDS, using PD and NPD, respectively.[243] In a study by van der Heijden et al., using Cohen's kappa (κ) to measure agreement, moderate to substantial agreement was found between TDS and FTF diagnosis (κ=0.55-0.73), there was moderate agreement between TDS and histopathology (κ=0.41-0.63) and almost perfect agreement between FTF and histopathology (κ=0.9). The agreement for management plans was reported as being only slight to fair with TDS (κ=0.19-0.29), but all 7 histopathologically diagnosed cases of skin cancer were nevertheless correctly managed.[244] In a study using images from the previously mentioned study, Tan et al. investigated the interobserver concordance of TDS, comparing the answers of five experienced dermoscopists regarding the diagnosis of different skin lesions. For melanoma, the agreement was very high for four of the dermoscopists (κ=0.81-0.97) but lower when adding the fifth dermoscopist (κ=0.38). For other diagnoses, varying concordances were found (e.g. κ=0.05-0.15 for SCC and κ=0.64-0.80 for SK).[245]

Possible explanations for the difference in results between studies include the study designs but also the setting in which they were conducted. One concern stated is that using TDS in PHC could be more difficult.[244]

During the latest decade, mobile TDS has been evaluated in a few studies. The first TDS study using cellular phones was published in 2007 by Massone et al. Eighteen consecutive patients were recruited, and when comparing FTF diagnosis with telediagnosis the diagnostic agreement for the clinical and dermoscopic images was 89% and 89-94% respectively.[246] In another early study on 113 skin tumours in 88 patients, Kroemer et al. found an agreement between mobile TDS and gold standard (histopathology if available, FTF diagnosis if not) of 90% with κ=0.84 for both clinical and dermoscopic images.[247] Both these studies used the camera of a mobile phone and dermoscopic images were acquired by simply holding the phone against the dermoscope. Börve et al. used a modern smartphone with a specifically designed dermoscope and a pre-installed application (the same smartphone-based TDS system as in Study I) and compared the decisions regarding diagnosis and management of two teledermoscopists and the FTF dermatologist with histopathology for 69 lesions. The diagnostic accuracy of FTF (66.7%) was significantly higher than that of one teledermoscopist (50.7%, p=0.04) but not higher than that of the other one (60%, p=0.52). The teledermoscopists provided adequate management decisions in 98.6% and 100% of the cases, respectively.[248] In 2016, a study was published by Hue et al. on the use of real time mobile TDS used in a skin cancer screening event, recruiting 289 patients with 390 suspicious lesions resulting in 412 images. For 53% of patients, no follow-up was considered necessary while melanoma was suspected in 12 patients and later confirmed in one case.[249] Equipment that can be used in DD monitoring and TDS can be seen in *figure 22*.

FIGURE 22. (a) A system used for total body photography (TBP) and digital dermoscopy monitoring of high risk patients. Standard positions for TBP can be seen on the wall behind the device. (b) Smartphone and dermoscope that can be used for mobile teledermoscopy.

With 816 referrals in 772 patients in the TDS group and 746 patients in the control group, Study I is the largest study on mobile TDS to this date.

In 2017, a systematic review was published by Finnane et al. that focused on TD/TDS specifically used for the diagnosis and management of skin cancer. It included 21 studies published after June 2009 (including Study I), most of them utilising TDS. Compared to the previous review (see section 1.7), the studies included are more likely to have used equipment relevant to the present date. It addressed the following three questions, with the following results:

1. How accurate is TD/TDS for skin cancer diagnosis, compared to usual care (FTF diagnosis)?

In total, TD/TDS was shown to be slightly inferior to FTF dermatology, with an agreement with the reference standard of 67%-85% for FTF and 51%-85% for TD/TDS. Other findings for TDS include diagnostic agreement with histopathology of 51%-92% while sensitivity and specificity for melanoma was found to be 96% and 62%, respectively. The diagnostic concordance with FTF when using TDS was 46%-94% and the treatment concordance with FTF was 66%-85% (κ=0.19-0.83).

2. Does TD/TDS save clinician and/or patient time, compared with usual care?

Several studies found shorter time to treatment for melanoma with TDS. One study also reported lower Breslow thickness for melanoma cases referred by TD (1.06 vs 1.64 mm, p=0.03) and a larger proportion of tumours staged as Tis and T1a (70.1% vs 56.9%, p=0.03) indicating earlier diagnosis and better prognosis.[250]

3. Are there barriers to adoption of TD/TDS in clinical practice for the diagnosis of skin cancer?

Regarding potential barriers for the implementation of TD/TDS, only a descriptive summary was possible due to the heterogeneous nature of the studies and their outcome measures. Among the findings, they reported high patient satisfaction, higher diagnostic difficulty for TD/TDS compared to FTF and the image quality was reported as low/bad in 1%-36% of the submitted cases.

Based on the results, the following was recommended[251], using criteria by Robson et al.:[252]

1. TD/TDS should be used for patients where it is not feasible to provide FTF consultation (Grade of recommendation, 2A, Quality of evidence B).
2. TD/TDS can be used as a triage tool to reduce waiting times to assessment (2A, B).
3. Currently available technology is suitable for TD assessment. Training of clinicians and consumers and/or patients should be considered to improve image quality (1, B).

Grade of recommendation: 1, strong recommendation: high-quality, patient-oriented evidence; 2A, weak recommendation: limited-quality, patient-oriented evidence; 2B, weak recommendation: low-quality evidence.

Quality of evidence: A, systematic review/meta-analysis, randomised clinical trials with consistent findings, all-or-none observational studies; B, systematic review/meta-analysis of lower-quality clinical trials or studies with limitations and inconsistent findings, lower-quality clinical trial, cohort study, case-control study; C, consensus guidelines, usual practice, expert opinion, case series.

In summary, they do not recommend replacing FTF visits with a dermatologist with TDS but rather to use it when FTF visits are not possible. Also, it can be used to improve triaging before a FTF visit with a dermatologist, to decrease time to treatment of malignant lesions, most importantly melanoma.

Relatively few studies have been conducted with the aim to compare TDS with paper referrals. In 2014, a systematic review was performed by the Health Technology Assessment Centre at Sahlgrenska University Hospital, focusing on this issue. There were seven studies included that compared the use of TD/TDS referrals with paper referrals or text-based e-referrals, some of which were focused on skin cancer and three using TDS (study I included). The main conclusions were that TDS can improve the triaging process and reduce the time to treatment for patients with suspected skin cancer, compared to standard paper referrals. Also, the number of visits to a dermatologist for benign tumours might be reduced. One main concern stated is the fact that a TBSE cannot be performed and cases of skin cancer may be missed. This risk is considered low. Because of limitations in the number and size of the studies, the quality of evidence is considered low for all reported outcomes.[253]

1.8.1 Methods and applications

The two main methods of TD/TDS that have been described are real-time (RT) and store-and-forward (SAF). The former is when there is direct interaction between the two parties involved in the consultation, often via video-conference, or a transfer of images simultaneous to a phone call. The latter uses a transfer of patient data such as images and text to be stored for later retrieval. Both methods have advantages and disadvantages, summarised in *table 8*. Currently SAF is the most common TD/TDS method. In some cases, a combination is used.

TABLE 8. Main differences between store-and-forward and real-time teledermatology/teledermoscopy.

	Store and forward	Real-time
Flexibility	High; participants partake independently of each other	Low; all participants must be available at the same time
Interaction	Delayed	Direct
Time needed	Short	Time-consuming
Costs	Cheaper	More expensive
Information	Medical history and images are stored and transferred, standardised forms can be used	Immediate clinical information acquired from the patient, follow-up questions possible
Effect on daily workflow	Low impact	Large impact, can interfere with workflow

Another way of dividing TD/TDS into different categories is by who is involved in the consultation.[254]

- Primary TD/TDS means that there is a direct communication between the patient and a dermatologist, PHC physician, or other health care provider, to reach a preliminary diagnosis or serve as a base for a referral.
- In secondary TD/TDS, the most common form, the patient usually consults the PHC physician and there is then a communication between the PHC physician and the dermatologist.
- Finally, tertiary TD/TDS is when a more general dermatologist consults a sub-specialist (e.g. an expert on dermoscopy of acral lesions) about a case.

1.8.2 Benefits and risks with teledermoscopy

Benefits

The potential benefits of using TDS for skin lesions of concern are discussed in the former section, with references. In summary, the benefits are the following:

- In areas that are isolated or lacking dermatologists, dermatological expertise could become available.
- Recommendations about management could be given over a distance, while only those that have lesions suspicious for malignancy need to be sent to a dermatologist.
- Patients with clearly benign lesions could be given a reassuring answer. The need for patients to travel far or take extra time off from work would decrease.
- If replacing less sophisticated types of referrals, such as the paper referral, triaging of referrals could be improved and patients with skin cancer could be treated more quickly.
- It could be easier to treat cancer at the first visit, thus decreasing the number of visits for those in need of surgery or other time-consuming treatments. It would be easier to allocate the right amount of time for surgery when one has seen the lesion that needs to be removed.
- When knowing a patient is coming with a melanoma it is also easier to plan for the correct clinical setting and psychological approach when meeting a patient with such a dangerous cancer.
- The more effective management and decreased number of visits could also mean saving time as well as money, both directly in the health care system and indirectly when patients do not need to take time off work and travel.
- If less unnecessary excisions are performed in PHC this could also save money and decrease the pressure on histopathology departments, which lack resources in Sweden.[15, 255]

Risks

Potential downsides or risks depend on what is being replaced with TDS, if it is used to replace FTF visits or mainly to replace paper referrals or other more basic forms of referrals.

One possible negative aspect of evaluating single skin lesions of concern with TDS, is that a TBSE may not be performed in cases where the TDS referral is sent back to the PHC physician, without recommending a

FTF visit with a dermatologist. TDS is therefore less likely to detect incidental cases of skin cancer, not noticed by the patient or the referring PHC physician. An article by Aldridge et al. that compiled results from two studies, including 1851 patients with skin lesions of concern, found that 14 of 38 detected melanomas were incidental findings. TBSE increased the melanoma pickup rate from 1.3% to 2.1%, indicating that not performing a TBSE could result in missing one in three melanomas.[256] Another study by Argenziano et al., focusing on the value of TBSE for patients with focused dermatological problems (not only skin tumours), concluded that the risk of missing a skin malignancy of any kind was 2.17% (95% confidence interval (CI) 1.25 – 3.47) if TBSE was not performed. Factors significantly increasing the probability of finding skin cancer during TBSE were age, male gender, previous NMSC, fair skin type, a skin tumour as the reason for consultation and the presence of an equivocal lesion on uncovered areas.[107] In a study from 2017, focusing on the issue of "unimaged melanomas" in a population made up of military veterans from the western USA, it was found that the patient had a such a melanoma in about 1 in 1000 TD/TDS consultations.[257] Another recently published study found incidental cases of skin cancer (BCC and SCC) in 3.6% 165 patients referred by TD.[258]

To limit this risk, it is important that patients with sufficiently high risk of skin cancer, most importantly melanoma (e.g. personal or family history of melanoma, large number of naevi, history of multiple NMSCs), are seen FTF by a dermatologist, regardless of the nature of the lesion in the TDS referral. Furthermore, those with malignant lesions in TDS should be referred to dermatology rather than other specialities. In these cases, a TBSE can then be performed by a dermatologist, minimising the risk of missing skin cancer. It is also important to consider that TDS limits the possibility to go through the diagnostic process listed in section 1.4.7, i.e. the cognitive, comparative, and interactive processes involved in a traditional FTF visit with a dermatologist. A proper comparison between a referred lesion and the other lesions of the same patient will not be possible and it is up to the referring doctor to add information about recent changes in a lesion or other factors that may affect how the TDS referral is judged, including the use of pigment-altering substances such as DHA. It is therefore important to make it mandatory to add relevant clinical information to TDS referrals. Also, including overview images of the patients' skin can, to some extent, make it possible to assess important factors such as pigmentary traits, degree of sun-damage and what type of lesions the patient has.

Different aspects of benefits and risks with TDS are part of the discussion of study II.

Image quality of digital images in TD/TDS

Another aspect related to the possible risks of TDS is the image quality. If the quality of the images sent through TD/TDS is too low, this could potentially result in mismanaged cases of skin cancer.

Initially, dermoscopic images consisted of regular developed photographs or photo slides. In the late 1990s, studies were conducted comparing regular photographs to compressed DD images and digitised images transmitted by telephone, showing the diagnostic information to be similar.[237, 259] This indicated that it was safe to let digital images become the most commonly used image type.

If the preliminary diagnosis and management plans for skin cancer is to be based mostly on digital dermoscopic images, it is reasonable to believe that the image quality is vital for this to be possible. However, there are very varying results regarding the effect of image quality on the diagnostic accuracy of TD/TDS. Early TDS studies by Piccolo et al. found diagnostic accuracy to be related to the experience of the teledermoscopist and diagnostic difficulty of the lesions rather than the image quality.[238, 239] Other studies have reached the opposite conclusion. A review article found high image quality as well as the use of dermoscopic images to be important factors to make TD/TDS effective in decreasing the need of FTF visits, and stated that trained staff should be used to acquire the images.[260] Another study compared the usefulness of TD images of good and poor quality and found the first group to be more likely to make early treatment of malignant lesions possible while safely delaying management of benign lesions.[261] In another study carried out in PHC, high image quality resulted in higher diagnostic and management accuracy compared to cases with images of bad or reasonable quality.[244]

In one study, comparing TD images of good and poor image quality there were definitions of what characterised images with the two levels of image quality, including both aspects of the images themselves (e.g. being in or out of focus, appropriate exposure or not, etc) and usefulness of the images (resulting in the ability to triage with confidence or not). Many other studies rate the quality of the included images without any stated definitions of image quality in the article.[239, 243, 244, 262] Some studies only state what aspects were considered important for image quality (focus, exposure and brightness) and not precise definitions of the categories used.[238] The lack of definitions for image quality makes it difficult to compare the studies.

Another problem when comparing the studies conducted to this date is that images have been acquired in different ways, with different equipment and by different personnel. Some studies have used specially trained staff, sometimes called melanographers, while in some, images have been acquired by dermatologists. This could have implications regarding the generalisability of their results to areas where this setup is not possible. Study III attempts to explore this by comparing images acquired in PHC with images of the same tumours acquired at the department of dermatology.

In a consensus statement published in 2016, that several dermatologists with focus on dermoscopy took part in, standards for skin lesion imaging were presented. This includes recommendations on lighting, field of view, image orientation, image formats and others. Related to dermoscopic images the following is stated:[263]

- ***Lighting:*** Using both polarised and non-polarised light is ideal. If only one image is obtained, polarised light is preferable.
- ***Field of view:*** The lesions should be balanced and centred. If the lesion is larger than the field of view, multiple images can be obtained.
- ***Image orientation:*** Dermoscopic images should, if possible, have the same orientation as any close-up or regional images of the same patient, e.g. primarily vertical or horizontal orientation. If multiple images are obtained over time, the orientation should be consistent.
- ***Resolution:*** For dermoscopic imaging, the level of magnification should allow clear visualization of small dots as well as regression structures (if present).
- ***Scale:*** A method to define the size of the lesion should be included. This can be achieved by a scale in the contact dermoscopic frame or a digital scale. If a physical scale is used this should not obscure or distract from the area of interest.
- ***Image storage:*** Images should be stored in formats that do not compromise the clinical quality, e.g. JPEG, TIFF, PNG, and RAW format.

2. Aims

The overall aim of this thesis was to study how the use of TDS affects the care of patients with suspicious skin lesions, from triaging, to establishing a diagnosis and planning treatment. We also aim to study safety aspects of DD and TDS as well as to point out risks and pitfalls so that they can be avoided. The specific aims of the studies included were:

- To study how smartphone TDS affects the triaging of suspicious skin lesions, the time to a first visit with a dermatologist and the time to treatment of malignant skin lesions.
- To assess the diagnostic agreement and interobserver concordance when assessing teledermoscopic referrals as well as the possibility to plan for treatment of skin cancer and safely resend referrals with benign lesions to PHC.
- To critically assess the image quality of dermoscopic images obtained in PHC and whether the image quality affects the possibility to reach a correct diagnosis.
- To investigate the effect of a sunless tanning product containing DHA on the dermoscopic features of pigmented skin lesions.

3. Methods

3.1 Study I

Subjects

The study population consisted of patients referred from the 20 PHC centres that took part in the study (12 in the Gothenburg area and 8 in Skaraborg) and sent TDS referrals to Sahlgrenska University Hospital (SUH) and Skaraborg Hospital (SH). In total, 816 TDS referrals from 772 patients were included in the study. The control group consisted of 746 consecutive patients referred by standard paper referrals from the other PHC centres in the same areas.

Methods

At the PHC centre, the TDS referrals were constructed by using a smartphone (iPhone® 4, Apple, Cupertino, California, USA) connected to a compatible dermoscope (Fotofinder Handyscope®, Fotofinder Systems GmbH, Bad Birnbach, Germany) and following the instructions in the smartphone application designed for the study (iDoc24 PRO, iDoc24 AB, Gothenburg, Sweden). One clinical image was acquired using the built-in smartphone camera and one dermoscopic image was taken after connecting the compatible dermoscope. Then, a standardised form containing relevant information about the patient history was filled out. The referral was then sent electronically and was evaluated by one of four dermatologists, two at SUH and two at SH. For all lesions, the priority given at the time of referral triage was compared with the priority stated in the regional guidelines *(see Table 2 in section 1.3.8)*. The time between the sending of the TDS or paper referral and the first visit at the department of dermatology and the primary treatment (if necessary) was determined. For the TDS referrals, the time to response from a dermatologist was measured. For the paper referrals, the time it took for the referrals to arrive at the hospital was quantified. The clinical outcome for the study group and the control group was compared, regarding how correct the priority was as well as the time required to offer a FTF visit and the time needed to treat the patient surgically when required.

Statistical analysis

Fisher's exact test was used to compare proportions between groups when the outcome was binary (e.g. if surgery was performed at the first visit or not). Mantel–Haenszel's test was used when comparing proportions between groups using stratification (e.g. the proportion of correctly triaged referrals for the different malignant diagnoses). Two-sample tests were performed using Wilcoxon's rank sum test (e.g. comparing time to surgery for different diagnoses). Statistical significance was set at $p<0.05$.

3.2 Study II

Materials

TDS and paper referrals were obtained from Study I, with the aim to randomly select 160 referrals, 80 TDS referrals and 80 standard paper referrals, evenly distributed between each of the four priority groups described in section 1.3.8. As there were only 17 paper referrals with intermediate priority (2-4 weeks), all the referrals in that group were used. Thus, 157 separate cases were included: 80 cases in the TDS group and 77 cases in the paper referral group.

Methods

The information from the TDS and paper referrals was entered into electronic forms that also included questions about the primary diagnosis, up to two differential diagnoses, the level of certainty for the selected diagnosis/diagnoses, the priority (including an option to resend the referral without seeing the patient FTF) and, if possible, a management plan (including planning for surgery at the first visit). The forms were evaluated by six dermatologists who did not have prior knowledge of the included cases, resulting in 942 answers for each question. The final clinical and histopathological (if available) diagnoses were known from Study I. If the primary diagnosis chosen by the evaluators was the same as the final diagnosis, this was defined as complete diagnostic agreement. If one of the differential diagnoses was the same as the final diagnosis, this was defined as partial diagnostic agreement. The final diagnoses were also used to define which priority group each case belonged to. The TDS group and paper referral group were compared regarding the suggested diagnosis, the priority given, the proportion of referrals with malignant lesions where it was possible to plan for treatment at the first visit and the proportion of referrals with benign lesions that could be resent safely to PHC without planning for a visit with a dermatologist.

Statistical analysis

Wilcoxon´s rank sum test (independent groups, categorical data) was used for significance testing of the difference in correct answers between the TDS and paper referrals. Since different evaluations of the same referral cannot be considered independent from each other, these statistical tests were not based on individual answers. Instead, each case in both groups was ranked based on how many correct answers were given (between 0 and 6 possible) and the ranks were used for significance testing. This decreased the chance of achieving statistical significance but is the correct way of making the comparison. To measure interobserver concordance, Fleiss' kappa was used.[264] This kappa value compares all evaluators as a group and does not require knowledge about which evaluator gave each individual answer. Suggestions about how to interpret Fleiss kappa, published by Landis and Koch, state that κ = 0.81-1.00 represent almost perfect agreement, 0.61-0.80 represent substantial agreement 0.41-0.60 moderate agreement, 0.21-0.40 fair agreement, 0.01-0-20 slight agreement while κ-values $\leq$ 0 represent poor agreement.[265] However, this way of interpreting the κ-values is not universally accepted. Statistical significance was set at $p<0.05$.

3.3 Study III

Materials

In 172 cases from Study I, the lesion photographed clinically and dermoscopically by PHC physicians and/or nurses and referred by TDS to SH was photographed a second time, by the dermatologist that saw the patient FTF or the assisting nurse. This resulted in 344 available dermoscopic images, in two sets, available for evaluation and comparison.

Methods

The TDS referral images were acquired in PHC, as described under Study I. The second set of images were acquired at the department of dermatology at SH by the dermatologist who saw the patient FTF, or sometimes by an assisting nurse. A Heine® D20 contact dermoscope (Heine Optotechnik GmbH & Co. KG, Herrsching, Germany) was used, coupled to a Canon® EOS D550 camera (Canon Inc., Tokyo, Japan). All images were evaluated by two dermatologists without prior knowledge of the cases. During the first sitting, they assessed the set of images acquired in PHC. Three to four weeks later, to avoid recall bias, the second set of images acquired at the department of dermatology were evaluated. While viewing the images, forms were filled out with questions regarding image quality, main diagnosis, up to two differential diagnoses and visible dermoscopic structures. Three levels for image quality were defined at the start of the study and were stated in the forms. An image of high quality was defined as having few or no apparent flaws, making it possible to diagnose the skin lesion. An image of intermediate quality was defined as having some technical flaws but providing enough information to be diagnosed. Finally, an image of low quality was defined as having many flaws and as being hard or impossible to use for diagnosing the skin lesion. At a later stage and in the cases where the main telediagnosis differed between the two images of the same tumour, the evaluators described any possible technical issues that might have explained this, including a difference in light/exposure, focus, pressure, zoom, polarised/non-polarised light or other technical issue.

Statistical analysis

Wilcoxon's signed rank test (for paired, categorical data) was used for significance testing of the difference between the two image sets. Statistical significance was set at $p<0.05$.

3.4 Study IV

Materials

This study included seven participants with 25 PSLs (range 1-6 lesions per patient) that were photographed, resulting in 38 dermoscopic images. Each lesion or part of a lesion was meant to be photographed at three different visits. However, one participant could not come to the last visit and one lesion was missed in another participant. Because of this, there were 105 images (38 images from visit 1, 38 from visit 2 and 29 from visit 3) to evaluate.

Methods

The included lesions were photographed with a Dermaphot lens (Heine® Optotechnik, Herrsching, Germany) coupled to a Canon® EOS D30 camera (Canon Inc., Tokyo, Japan) before application of the sunless tanning product containing DHA. The product was applied to a specified area of skin, on the face or on the body, containing one or more PSLs. The application was carried out by a dermatologist at the first visit and then by the participant, once daily, for a further three days. The participants returned for two follow-up visits, one week and 1-2 months after the first application of DHA. The lesions were photographed again during these visits. Two dermatologists assessed the images separately and answered questions about visible differences between the images acquired before and after DHA application and whether this difference remained at the last visit. They

also rated all images based on the level of suspicion for malignancy and stated which dermoscopic structures were found in each image.

Statistical analysis

For significance testing regarding the proportion of images with new dermoscopic features and images rated as equivocal before and after DHA, McNemar's test was used. This is a test for categorical data with binary outcomes. It was possible to use this statistical method to compare how the images were rated for malignancy, since all answers given were either benign or equivocal and no lesions were rated as malignant. Statistical significance was set at $p<0.05$.

3.5 Ethical considerations

Ethical approval from the regional ethics boards was obtained for study I-III. Study IV was conducted in line with national regulations but approval from an ethics board was not considered necessary as it was a small pilot study and the product tested was a readily available cosmetic product.

4. Results

4.1 Study I

Priority

It was possible to correctly triage TDS referrals to a larger degree than paper referrals. With TDS, 22.6% more referrals were given low priority, a difference mainly seen at SH, where paper referrals with skin tumours were often triaged as having medium or high priority. Since paper referrals at SH were systematically overprioritised to not miss malignancy, no further analysis of the accuracy of the triage process was carried out for SH paper referrals.

With TDS, all 19 patients with invasive melanomas were correctly given high priority and all 16 patients with melanoma in situ were given medium priority or higher, in accordance with the guidelines. With paper referrals, 3 out of 4 patients with invasive melanomas (75%) sent to SUH were incorrectly given a medium or low priority and 3 out of 5 patients with melanoma in situ (60%) were incorrectly given low priority. The difference was statistically significant for both diagnoses (p=0.0023 for melanoma and p=0.0075 for melanoma in situ). A difference was also seen for patients with SCCs, as 11 of 17 (65%) were correctly given high priority in the TDS group compared to 2 of 5 (40%) in the control group at SUH. For SCC in situ, 5 of 7 (71%) patients in the TDS group were correctly given high or medium priority, compared to 4 of 9 SCC in situ (44%) in the control group at SUH. However, for these diagnoses, the difference was not statistically significant (p=0.61 for SCC and p=0.36 for SCC in situ).

The prioritisation of benign naevi and DN also differed between the TDS and paper referrals at both hospitals. Benign naevi in the TDS group were triaged correctly as having low priority in 86% of the cases, which was significantly more often than the 74% of benign naevi correctly triaged in the control group (p=0.011). For DN, the teledermoscopists were more careful with their triage decision giving the TDS referrals higher priority than necessary (medium or high) in 67% of the cases in comparison with only 36% of the control cases (p=0.053). There were no significant differences between TDS and paper referrals regarding the correctness of the triage decisions for patients with AKs, BCCs or SKs.

Time to first visit and surgical treatment

Within a median time of 1.8 hours, the TDS referrals were evaluated and a response was sent to PHC (range 2 minutes to 46 hours). Almost all TDS referrals (98%) were answered within 24 hours. For paper referrals, it took a median time of 4 days (range 0-82 days) for the referrals to reach the hospital, and a response was sent after the patients' FTF visit. The time to the first visit with a

dermatologist was significantly shorter for patients with a final diagnosis of melanoma, melanoma in situ, SCC, SCC in situ or BCC if referred by TDS compared to paper referral (p<0.0001). A significant difference was also seen for waiting times to receive surgical treatment for patients with melanoma (p<0.0001), melanoma in situ (p=0.028), SCC (p=0.046), SCC in situ (p=0.022) and BCC (p<0.0001) *(Table 9)*. Most importantly, TDS made it possible to see and perform primary surgery for the patients with melanoma after a median time of 9 days, compared to those referred by paper referral who had their first FTF visit after 14 days and received surgery after 35 days. With TDS referrals, the median waiting time for diagnosis and treatment for all patients with malignant lesions was 36 days, compared to 85 days with paper referrals (p<0.0001). No significant differences were found in the waiting times for diagnosis and treatment for patients with benign lesions or AK.

TABLE 9. Median number of days that patients with malignant lesions requiring surgical treatment had to wait for a first visit with a dermatologist and the first excision in the smartphone teledermoscopy and traditional paper referral groups

	Group	Melanoma	Melanoma in situ	SCC	SCC in situ	BCC
Median time to first visit, days	TDS Paper	9 14	10 17	13 21	13 96	28 34
Median time to surgery when required, days	TDS Paper	9 35	12 48	15 62	13 118	34 89

TDS, teledermoscopy; Paper, standard paper referral; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

Patients in the TDS group were to a larger degree able to receive primary treatment on a single visit, 93.4% of the cases (95% CI, 91.5–95.0%) as compared to 82.2% of the paper referral cases (95% CI, 79.2–84.9%). The difference was very clear for many of the malignant diagnoses, being statistically significant for melanoma, SCC and well as in the cases of SCC in situ and BCC that were treated surgically. For melanoma in situ there was a non-significant difference *(Table 10)*.

TABLE 10. Proportion of patients with malignant diagnoses that were treated surgically on the first visit with a dermatologist.

Diagnosis	TDS, %	Paper, %	p-value
Melanoma	84	13	***0.0002***
Melanoma in situ	69	29	***0.17***
SCC	71	18	***0.018***
SCC in situ	100	25	***<0.0001***
BCC	76	22	***0.048***

TDS, teledermoscopy; Paper, standard paper referral; SCC, Squamous cell carcinoma; BCC, basal cell carcinoma

Incidental findings and melanoma prognosis
After carrying out TBSEs, malignant incidental findings were discovered in 117 of the TDS referral patients (14%) and 97 of the paper referral patients (13%), respectively (p=0.46). The great majority of these incidental findings were BCCs and AKs, but 6 additional MM in situ were found in the TDS group as well as 4 invasive MMs, two MM in situ and one invasive SCC in the control group.

In the TDS group, 46% of the malignant melanocytic lesions were in situ, compared to 35% in the paper referral group. Of the invasive melanomas, the median Breslow thickness was 1.0 mm compared to 2.2 mm in the paper referral group. The number of cases was too small to analyse potential prognostic improvement with TDS

4.2 Study II

Diagnostic agreement
In the TDS group as a whole, complete diagnostic agreement between the telediagnosis and the final diagnosis was achieved in 64% of the evaluations, compared to 47% with paper referrals (p=0.0019). Partial diagnostic agreement was achieved in 81% of the evaluations with TDS and 70% of the evaluations with paper referrals (p=0.13).

When grouping malignant and premalignant diagnoses together, there was a statistically significant difference regarding the proportion of referrals with complete diagnostic agreement (67% with TDS vs 53% with paper referrals, p=0.048) but not regarding the partial diagnostic agreement (83% vs 79%, p=0.82). For invasive melanoma, complete diagnostic agreement was achieved significantly more often with TDS than with paper referrals, 91% compared to 50% of evaluations (p=0.015). The difference was also statistically significant for SCC in situ but not for melanoma in situ, SCC, BCC, and AK. The difference in diagnostic agreement between the groups was statistically significant for malignant melanocytic lesions (p=0.021) but not for malignant non-melanocytic lesions (p=0.57).

For the benign diagnoses grouped together, TDS resulted in complete and partial diagnostic agreement significantly more often than with paper referrals (60% and 77% with TDS vs 29% and 47% with paper referrals, p=0.0027 and 0.0044). Likewise, for benign diagnoses that were considered unprioritised according to the triage guidelines (CN, SK, SL, dermatofibroma and angioma), complete and partial diagnostic agreement based on the TDS referrals was reached significantly more often (63% and 74% with TDS vs 29% and 47% with paper referrals, p=0.0023 and 0.016).

Interobserver concordance
The interobserver concordance was calculated regarding the primary diagnosis, comparing all six evaluators as a group. The agreement could be considered moderate for both referral methods, as Fleiss' kappa scores were 0.52 for TDS and 0.50 for paper referrals. The interobserver concordance was higher for correctly classifying lesions as benign or malignant (κ=0.67 for TDS vs 0.55 for paper referrals) and melanocytic or non-melanocytic (κ=0.88 for TDS vs 0.74 for paper referrals).

Correctly and incorrectly resent referrals
In the referrals with a benign final diagnosis, TDS resulted in 43% of the evaluations recommending that the referral be resent to PHC without a FTF visit compared to less than 1% with paper referrals (p<0.001).

In the TDS group, the option of resending the referral was incorrectly chosen for

lesions with malignant/premalignant diagnoses in 8 of the 318 evaluations (2.5%). The TDS referral was triaged as unprioritised in five assessments of four different cases of melanoma in situ (6% of evaluations). One assessment of a referral for a BCC and two assessments of a referral for an AK were also triaged this way. This problem did not occur in the paper referral group. Three of the cases can be seen in *figure 23*.

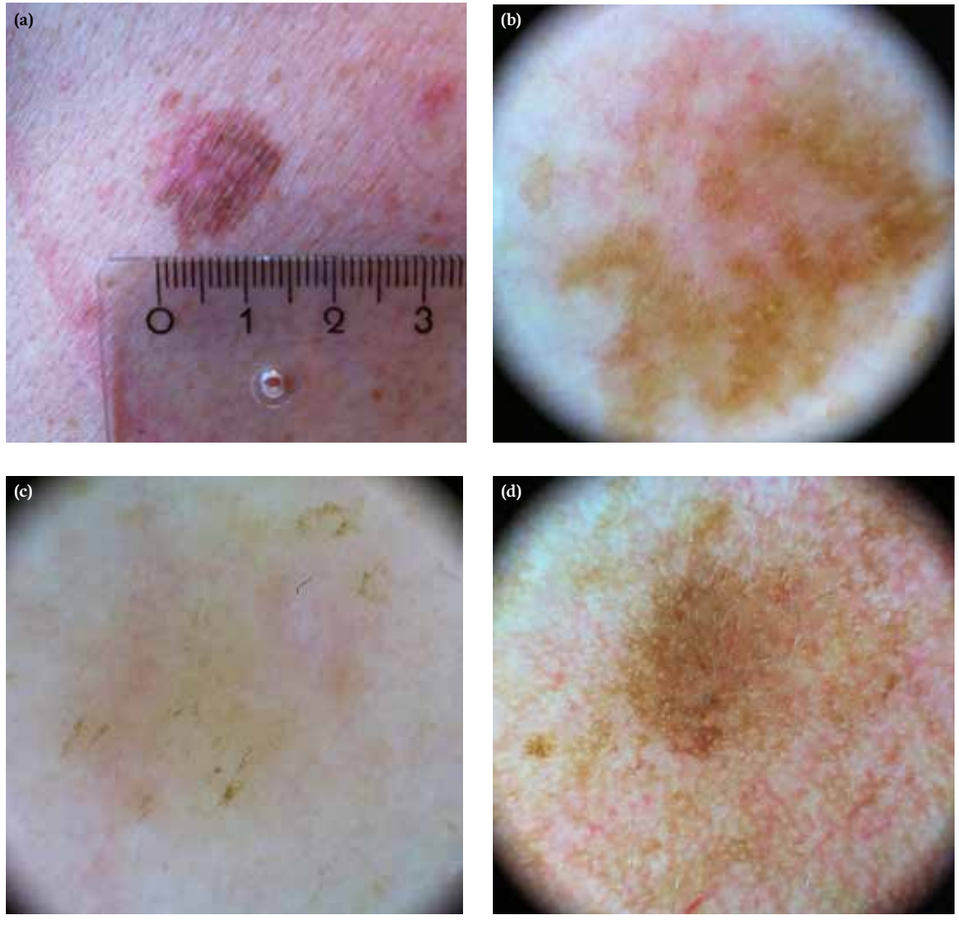


FIGURE 23. Incorrectly resent referrals with malignant/premalignant lesions. Upper images showing a case of melanoma in situ resent by one evaluator. Clinical image (a) showing a large, brown and pink lesion, while the dermoscopic image (b) shows pigment network and a hypopigmented area with vessels. Together the images should give enough information to make it clear that a face-to-face appointment must be booked. Lower images show a case of basal cell carcinoma (c) with very few features to evaluate and a case of pigmented actinic keratosis (d), both cases resent by one evaluator.
Photo: *Johan Dahlén Gyllencreutz*

General prioritisation and triage of melanoma
The triaging decisions made by the evaluators were completely correct in 51% of the TDS evaluations, compared to 38% in the paper referral group (p=0.042). The largest difference was found for invasive melanoma, where TDS resulted in the correct prioritisation in 98% of the evaluations (only one incorrect evaluation) compared to 62% with paper referrals (p=0.012). For the other malignant and benign tumours, differences were more modest.

Planning for surgery at the first visit
With TDS it was possible to plan for surgery at the first visit significantly more often than with paper referrals, for all tumour types where excision is needed. Once again, the largest difference was seen for melanoma, where TDS resulted in this option being chosen in 91% of the evaluations, compared to 36% with paper referrals (p<0.001). When combining the diagnoses where surgery is always recommended (melanoma, melanoma in situ and SCC), TDS made it possible to plan for surgery at the first visit after 71% of evaluations as compared to 39% with paper referrals (p<0.001).

4.3 Study III

Image quality
The most common answer given regarding image quality was high, for both images types. In fact, only 1.2-4.7% of images were rated as having poor image quality. The images acquired at PHC were found by both evaluators to be of slightly lower quality but the differences were not statistically significant, with p-values of 0.25 and 0.28 respectively for the two evaluators.

Diagnostic agreement with final diagnosis
The two evaluators achieved complete diagnostic agreement with the final diagnosis in 82.6-84.3% of the cases and a partial agreement in 92.4-97.7% with the two image types. There was no statistically significant difference in diagnostic agreement between the image types (p=0.37 and 0.99 respectively, for the two evaluators).

Interobserver concordance
One evaluator rated the images quality of both image types significantly higher than the other (p=0.00021 and 0.0013 for the PHC and dermatology images respectively). There was no significant difference in how often the two evaluators reached total or partial agreement with the final diagnosis (p=0.72 and 0.80 for the PHC and dermatology images respectively).

Technical issues related to difference in diagnosis
In 47 of the cases (27%), one or both evaluators suggested a different main diagnosis for the two different images of the same lesion. The three main reasons for this difference in diagnosis they could agree upon where image focus, pressure applied and amount of zoom used.

4.4 Study IV

Dermoscopic differences seen after DHA
For most lesions, there was a difference in dermoscopic features before and after the use of DHA. The two evaluators noted differences in 36 and 34 of the 38 images, respectively. In the pictures taken during the third visit (after 1–2 months) these features were seen in only two images and one image, respectively.

Equivocal lesions and dermoscopic features
The two evaluators found significantly more facial lesions to be equivocal after the use of DHA than before, (11 vs 3, p=0.021 and 18 vs 5, p=0.001). They also found follicular pigmentation (FP) in these lesions significantly more often after DHA use (21 vs 3, p<0.001 and 18 vs 4, p<0.001). An example of a lesions with FP can be seen in figure 24. For the lesions on the body, no statistically significant difference regarding the number of equivocal lesions was found. New dermoscopic features were seen mainly as globules in raised lesions. In equivocal lesions, both evaluators recommended a biopsy.

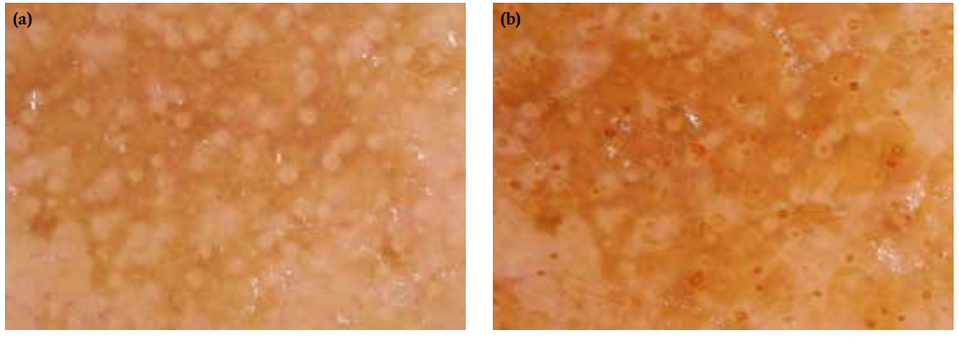


FIGURE 24. Facial lesion before (a) and after (b) the use of dihydroxyacetone. Apart from a stronger orange-brown colour, multiple pigmented follicles can be seen. ***Photo:*** *Johan Dahlén Gyllencreutz*

Agreement

The two evaluators were in agreement in 95% of cases for the observed difference in dermoscopic features seen one week after the first application of DHA and in 96% for the difference seen after 1-2 months. Regarding the number of equivocal lesions, the agreement was 71% for the lesions on the body and 75% for the lesions on the face. The agreement for observed FP was 88%.

5. Discussion

5.1 Study I

Methodological considerations

One aspect that is important to point out is that patients were not randomised to TDS or paper referral, as such a system was not possible to construct during the time allocated for the study. The 20 PHC centres that participated in the study were asked to use only the new referral method but it was not possible to make sure they did that in 100% of cases. All other PHC centres in the two regions used the standard paper referral. The lack of randomisation may have contributed to the fact that there were some differences between the study group and the control group regarding the distribution of diagnoses. The main difference was that there were more referrals for naevi in the TDS group, while the number of AKs were greater in the control group. This should not have affected the main results since they were focused on more malignant diagnoses. It is possible that the PHC physicians at the participating PHC centres may have been more proactive in trying to identify melanocytic lesions for TDS referral when having been equipped with a dermoscope. Patients with suspicious-looking naevi may even have been referred via TDS to avoid an unnecessary excision within PHC. Such behaviour may actually be another advantage of smartphone TDS as it would add cost-effectiveness to the management of patients with skin lesions of concern.

The PHC centres that took part in the study were also not randomly selected, but a relevant difference in the doctors sending TDS and paper referrals is unlikely, as both large and small PHC centres located in both urban and rural areas were represented in both groups. The TDS referral evaluators had experience in the use of dermoscopy that may have been considered greater than the main experience of the paper referral evaluators. However, only one of the evaluators had formal training in dermoscopy through the University of Graz at the time of the study. The rest were self-taught through clinical work. It is possible that the results of this study are only attainable with proper training and/or experience of the dermatologists assessing TDS referrals, something that should be considered when implementing this technique.

Another limitation to the study was the fact that we could not influence the traditional triage protocol used by SH. Most referrals were given high or medium priority. Only 3.2% of control referrals at SH were given low priority as compared to 75.8% of SUH's control referrals, 59% of SH's TDS referrals and 72.7% of SUH's TDS referrals. The triage decisions at SH dramatically shifted towards lower prioritisation when their dermatologists assessed TDS referrals containing clinical and dermoscopic images and

standardised clinical information as opposed to the limited diagnostic information provided by paper referrals.

An issue that is common for TDS/TD studies, and also a factor here, is the lack of a strong control for benign lesions. All lesions that were considered benign on FTF evaluation were defined as such in the study. There is a theoretical risk that there were malignant lesions in that group, too early in their development or too featureless to diagnose, but the same risk exists with paper referrals. An alternative would have been to have an expert in the field of dermoscopy control all images belonging to this group of lesions or to include follow-up in these cases. However, the latter alternative would have been difficult to realise since it could affect the waiting times for other patients.

It is also possible for the opposite problem to occur in TDS studies. If the dermatologists evaluating the TDS referrals are more experienced in dermoscopy, they might be able to correctly diagnose early or featureless malignant lesions correctly, while the possibly less experienced dermatologist seeing the patient FTF might not. In those cases, the clinical diagnosis chosen by the less experienced doctor will be considered correct, regardless of which diagnosis is truly correct. There were a number of cases in this study, where the telediagnosis and histopathological diagnosis were in agreement when the clinical diagnosis after the FTF visit was not. Looking at melanoma and melanoma in situ, there were five cases (14.3%) where the telediagnosis was correct but the primary clinical diagnosis was benign (being DN in three cases, CN in one and SK in one). It can be speculated that some of these lesions might not have been excised or biopsied, had that not already been planned for by the teledermoscopist. One such cases is seen in *figure 25*.

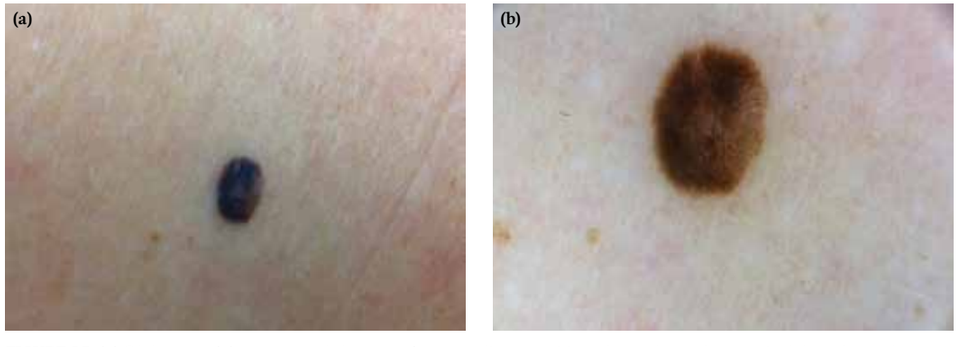


FIGURE 25. (a) Clinical and (b) dermoscopic images of a case with correct telediagnosis and incorrect clinical diagnosis. Clinically, the lesion appears almost bluish-black while dermoscopy reveals mostly brown pigmentation but also negative network, at 3 o'clock. The telediagnosis was melanoma and the patient was triaged for surgery at the first visit. The clinical diagnosis after the face-to-face visit with another dermatologist was "dysplastic" naevus. Histopathology showed a melanoma in situ ***Photo:*** *Johan Dahlén Gyllencreutz*

Some of the difference in time to treatment between TDS and paper referrals was a result of the delay that the paper referrals cause by being sent by regular mail. It can be argued that TDS should have been compared with an electronic, text based referral. However, such a comparison is irrelevant in the region where the study was conducted, as it does not exist and it has not been possible to implement even five years after the study was completed. Also, implementing an electronic referral that does not make it possible to send images would result in most of the potential of the referral to be lost. Another part of the difference in time to treatment takes place between the first visit with a dermatologist and the time for surgery. Thus, a major part of the difference found in this study is a result of knowing the diagnosis and being able to plan for proper treatment at the first FTF visit. This also means that if TDS is implemented as "only a triaging tool", without changing other aspects of the management of patients with skin cancer, some benefits are likely to be lost.

General discussion

Our results show that smartphone TDS referrals provide faster management of patients with skin cancer and allow for less inaccurately triaged referrals for patients with skin lesions of concern, compared to today's paper referrals without images. The use of TDS also resulted in fewer patients triaged to an urgent visit unnecessarily. The median time to diagnosis and treatment for all skin cancer types was also significantly shortened using TDS. In addition, TDS referrals resulted in more patients being able to receive their diagnosis and primary treatment on their first FTF visit with a dermatologist.

The triage decisions made based on TDS referrals were more reliable than those made based on traditional paper referrals. No patients with melanoma or melanoma in situ in the TDS group were triaged incorrectly and fewer patients with SCC and SCC in situ were given a lower priority than recommended when comparing with SUH's paper referral group, which had the same triage protocol as the TDS group.

Another clear benefit of TDS referral systems is that it more often allows the dermatologist to plan for surgical treatment on the patient's first visit to the hospital. With smartphone TDS referrals, first-visit surgical management was possible for 84% of patients with melanoma with a median waiting time of 9 days, which was almost 4 weeks earlier than patients with melanoma in the paper referral group. Surgical treatment on the first visit also resulted in more patients in the TDS group with melanoma in situ, SCC, SCC in situ and BCC avoiding unnecessary re-visits to the hospital. Similar results have been found by Morton et al. who reported that 91% of patients could receive definitive care at their first visit to a specialist with TDS, compared to 63% by the traditional referral pathway.[266]

When patients are referred from a PHC physician to a dermatologist for a skin lesion of concern, other malignant lesions are sometimes found after a TBSE. Such incidental findings were found in 13-14% of the patients in our study, regardless of the referral type, and in total there were 12 incidental melanomas found in 1518 patients (0.8%). Both these results are in line with previous studies.[256, 267] If TDS referrals are to be used to avoid unnecessary hospital visits, the referring PHC physicians should be reminded that a TBSE is important. This sort of reminder can be added to the standardised responses sent back through the TDS platform.

Although the number of patients diagnosed with melanoma or melanoma in situ in this study was limited, patients with such lesions had more favourable prognostic characteristics in the TDS group with a greater percentage of in situ lesions and thinner invasive melanomas. While some of this

difference may have been random, it is in line with another study, where patients referred by TD also had thinner melanomas, 1.06 vs 1.64 with paper referrals.[250] With a larger cohort of patients, smartphone TDS referrals may prove to be capable of providing improved prognosis for melanoma patients by shortening the doctor's delay.

This is the largest study to date on patients comparing the clinical outcomes resulting from triage through either TD/TDS or traditional letter referral systems in a real-life clinical scenario and also the largest study on mobile TDS. In conclusion, smartphone TDS referrals allow for faster and more efficient management of patients with skin cancer as compared to traditional paper referrals. Moreover, the method is safe and leads to fewer incorrectly triaged skin cancer patients. With the rising incidence of skin cancer, the lack of dermatologists and the number of unnecessary excisions carried out within PHC today in many European countries, smartphone TDS referrals can provide substantial improvements to the clinical pathway for patients with skin lesions of concern.

5.2 Study II

Methodological considerations

The difference in diagnoses between the study group and control group in study I carried over to this study. One effect of this, together with the random selection of cases, was that there were no referrals with the final diagnosis of DN in the paper referral group. For the diagnosis of AK, the paper referrals mainly consisted of typical and/or multiple lesions, while the TDS referrals for AKs were mostly single lesions where the clinical diagnosis was more malignant. The referrals selected to be part of this study were randomised so that all four priority groups were equally represented rather than with the aim of emulating reality. This was to make it easier to draw conclusions about all diagnoses but differs from the distribution of diagnoses in real life. All answers in this study were anonymous and because of this, there was no way of looking at the answers of a single evaluator. It is therefore not possible to know if the decision to resend referrals with melanoma in situ, for example, were mostly made by one individual or more evenly spread out among the six different evaluators.

Unlike study I, the results from this study is based on evaluations of internet forms, rather than the outcome of actual patients. Knowing that their decisions regarding diagnoses and triaging would not affect actual patients might have affected the answers given by the evaluators.

General discussion

In this study, several benefits with TDS referrals over traditional paper referrals were found. TDS to a larger degree made it possible to reach diagnostic agreement with the final diagnosis, to make adequate triage decisions, and to plan for direct surgical care of the patient (before the FTF visit) when needed.

The difference in diagnostic agreement was most apparent for melanoma, where it was significantly higher with TDS. With most melanomas discovered at the evaluation of the referral, TDS can make it possible to correctly triage and plan for surgery at the first visit. For melanoma in situ, the difference in diagnostic agreement was not significant, and a few decisions to resend TDS referrals without planning for a FTF visit were made, something that did not occur with paper referrals. This points out one of the most important risks with TDS as it could delay proper diagnosis and treatment for these patients.

In total, there were six cases triaged by evaluators to be resent without planning for a visit with a dermatologist. The cases (four cases of melanoma in situ, one case of BCC and one case of AK) were, in general, dermoscopically feature-poor. When using TDS, it is crucial that there is a low threshold to prioritise TDS referrals to a FTF visit with a dermatologist, especially if the lesion of concern is of melanocytic origin.

For several of the other premalignant/malignant diagnoses the difference between TDS and paper referrals was not statistically significant. Different likely reasons can be found to explain this. For SCC, only 4 of 11 cases in the TDS group received the clinical diagnosis of SCC after the FTF visit to a dermatology clinic, compared to all 9 cases in the paper referral group. For BCC and AK, the explanation could be that these common types of tumours are relatively easy for PHC physicians to recognise and thus to correctly describe in text. For AK, another explanation is selection bias. In the paper referral group, 9 of 11 cases were multiple or typical AK lesions not requiring a biopsy, whereas the TDS group contained single lesions in which biopsies were necessary for a proper diagnosis in three the of six cases.

Interestingly, the difference between the referral methods was much more apparent for SCC in situ. This might be explained by the fact that these tumours often have dermoscopic clues recognised by trained dermoscopists, but are much more difficult for a PHC physician to clinically differentiate from an AK.

For benign lesions, TDS made it possible to reach diagnostic agreement significantly more often than paper referrals and for the unprioritised lesions, it was possible to send referrals back to PHC to a much larger extent. The time saved by avoiding FTF visits for clearly benign lesions could be used to shorten waiting times to dermatologists in general and it could increase the cost-effectiveness of the method.

TDS did not achieve a significantly higher interobserver concordance, when looking at all diagnoses. There is no definite consensus on how to interpret Fleiss' kappa values, but both referral methods seem to show a moderate interobserver concordance. Two things could have contributed to the lack of significant difference in interobserver concordance. When comparing common diagnoses, such as BCC and AK, the correct diagnosis is often listed in the referral, making it more likely for many evaluators to choose that diagnosis. There were also many paper referral cases in which most of the evaluators chose the same incorrect diagnosis, making interobserver concordance higher.

Other studies have found similar results regarding diagnostic agreement between TDS and clinical and histopathological diagnosis, reporting complete agreement of 52-74% and partial agreement of 71-82%, depending on the study design, what types of lesions were included, and how agreement was defined.[241-243] When looking at interobserver concordance, others have reported Cohen's kappa values between κ = 0.05 and 0.97 depending on the diagnosis, generally being the highest for melanoma.[244, 245] This is in line with TDS in this study, where the interobserver concordance was moderate for all diagnoses grouped together but where most evaluators made the same, correct choices regarding the diagnosis of melanoma.

Lessons to be learned

When studying the results and the data in this study, it is possible to get ideas that are

useful when implementing TDS referrals, or that have implications regarding management of skin cancer in Sweden. Since it was not possible to cover all of this in the discussion section of the article, some of the ideas will be listed in *table 11*:

TABLE 11. Possible ideas based on data from Study II.

Diagnosis	Interesting finding	Lesson/idea
Melanoma	1. Main diagnosis correct in 91% of TDS evaluations, 91% booked for surgery 2. Only one incorrect decision regarding priority, a lesion thought to be a pigmented BCC by one evaluator	1. It's almost always possible to optimise treatment for melanoma with TDS 2. Consider prioritising pigmented BCC higher, at least if nodular lesion
Melanoma in situ	1. One case incorrectly resent by two evaluators and in 3 cases by one evaluator (5 evaluations; 6%) 2. A melanocytic lesion was considered in 2 of the 5 evaluations, whereas, in the other 3, the lesion was thought to be non-melanocytic	1. Keep a low threshold to offer FTF visits for patients with AMLs 2. Be careful when assessing feature-poor lesions, which may be melanocytic
SCC	Only 4 of the 11 cases in the TDS group had a clinical diagnosis of SCC	Lesions that are difficult to diagnose clinically will also be difficult to triage with TDS
SCC in situ	A large difference in correct main diagnosis, 75% for TDS vs 21% for paper referrals	Difficult for PHC physicians to recognise SCC in situ, whereas TDS can help in differentiating from AK
BCC	In 8 of 9 paper referrals, BCC is stated as a suspected diagnosis	For common tumours, that the PHC physicians recognise, paper referrals work well. For TDS to work even better, one or more suggested diagnoses could be included in the referral.
AK	In 10 of 11 paper referrals, AK is listed as a suggested diagnosis and in 7 of these cases, AK was the only diagnosis mentioned	PHC physicians often recognise AKs and could learn to treat them themselves
Un-prioritised	With TDS, 43% of referrals could be resent, compared to under 1% with paper referrals	TDS can free up time to manage patients with malignant skin lesions

TDS, teledermoscopy; SCC, Squamous cell carcinoma; BCC, basal cell carcinoma; AK, actinic keratosis; FTF, face-to-face; AML, atypical melanocytic lesion; Unprioritised: common naevus, seborrheic keratosis, dermatofibroma and angioma.

Another interesting finding is that the concept of differential diagnosis seems to mean something different when using TDS compared to paper referrals. For the cases with a final diagnosis of melanoma, where melanoma is a differential diagnosis rather than the main diagnosis, all cases were nonetheless triaged as melanoma, with high priority. In contrast, when looking at the same thing for paper referrals, only 8 of 21 evaluations with a differential diagnosis of melanoma received high priority. In the study, the partial diagnostic agreement for melanoma with paper referrals is listed as 82% but if only cases with the correct priority were to be included, that number would be 62%.

5.3 Study III

Methodological considerations

A strength of this study is the fact that the three levels of image quality were clearly defined. This can make it easier for readers to understand the results as well as compare them to other studies on image quality, if definitions are available. A choice was made to base the definition mainly on the level of usefulness of the images for diagnosing skin lesions. The images rated as having intermediate image quality could have flaws (e.g. part of the lesion not shown or being unfocused) but were still considered useful in diagnostics. A potential risk of defining image quality this way, is that a lower image quality is assigned for lesions that are in themselves more difficult to diagnose, e.g. related to hyperkeratosis or crusts covering most of the lesion. It was therefore stated that lower levels of image quality should not be used in such cases.

Since the equipment used in PHC and at the department of dermatology was not the same, we cannot isolate the exact effect of having a PHC physician acquiring the images for TDS referrals. The reason for this choice of equipment was that we wanted to critically appraise the smartphone TDS system used in study I, by comparing it with something as close as possible to the standard equipment used in clinical practice. This resulted in the choice of using a Heine D20 dermoscope (the most commonly used dermoscope at the department of dermatology, SH) together with a camera recommended by Heine. When planning the study, both the equipment used in PHC and the PHC physicians' lack of experience in dermoscopic photography were considered factors with potentially negative impact on image quality. However, it appears that the user-friendly equipment might instead have balanced out the inexperience to some degree.

It was not possible to blind the evaluators to which type of image they were viewing since the TDS referral images had a rounded black border that couldn't be removed and the other set of images did not. Therefore, it was also not possible to mix images from the two sets and the viewing had to be done one image set at a time. When viewing the images acquired at the department of dermatology, the evaluators had therefore already seen the PHC images of the same lesion. Nevertheless, the relatively large number of cases and the 3-4 weeks between the viewings should have limited the risk of recall bias.

General discussion

The primary aim of this study was to evaluate if the use of dermoscopic images acquired in PHC can affect TDS in a negative way, and if this could lead to an incorrect preliminary diagnosis. The images acquired with a smartphone in PHC were found to have slightly lower image quality than images of the same lesions acquired by dermatologists with greater experience in dermoscopic photography. However, the difference was not statistically significant and only 1.2-4.7% of the images were rated as having low quality, independently of who took them and what equipment was used. The finding regarding image quality is in line with some studies[262] but in contrast to one study in which 36% of the images were considered to have bad quality.[244]

One evaluator rated the images of both types as having significantly higher quality than the other, perhaps indicating that image quality is something subjective, even when definitions are given. Image quality was based partially on how difficult it was to use the images for diagnosing skin lesions. Although rating image quality systematically

lower could be a result of finding the evaluations more difficult, in this study it did not affect how often the correct diagnosis was chosen.

There was no significant difference in complete and partial diagnostic agreement with the final diagnosis between the image sets and the two image types allowed for a very high interobserver concordance in terms of the two evaluators' suggested diagnoses.
The technical issues noted as influencing the ability to choose the correct diagnosis included aspects that can be improved with training/education (e.g. making sure the image is in focus or applying the right amount of pressure). Other aspects were directly related to the equipment used (e.g. the amount of zoom was fixed for the dermatologists' camera). The use of polarised or non-polarised light made a difference in a few cases but did not play a major role.

5.4 Study IV

Methodological considerations

This was a small pilot study that was not meant to be used to draw any final conclusions but rather to form hypotheses. There were no controls in the study, but it is unlikely that the findings were caused by chance or by another agent than DHA. The evaluators did not know which images were taken before or after DHA but knew the study was ongoing, which might have contributed to the fact that no lesions were rated as malignant. Instead, the lesions with new dermoscopic features were rated as equivocal. A different result may have been reached if the images in this study had been mixed with images of other lesions where cases of LM were included, as well as having evaluators who did not have any knowledge of the study.

General discussion

How tanning agents, such as DHA, affects dermoscopic features remains largely unexplored. A small number of reports have shown that DHA can affect dermoscopy of PSLs and even simulate melanoma.[124, 127] We found that the use of DHA can lead to temporary changes in dermoscopic features in PSLs and that, for facial lesions, there may be a risk that the use of DHA can affect how the lesion is rated and lead to unnecessary biopsies. For example, the FP that was seen after application of DHA was somewhat similar to the types described in LM.[8, 40] Nevertheless, the colour of the FP was more orange-brown than the slate-grey often seen in LM. In a study by Pralong et al., FP that could be symmetrical and/or asymmetrical, was found to be among the most common features in LM/LMM.[268] In naevi, the dermoscopic changes did not affect how the lesions were rated, something that could have been affected by the smaller number of lesions in this group.

6. Conclusion

- The use of smartphone TDS instead of paper referrals can make triage of skin cancer safer and decrease the time to a first visit and to treatment. Fewer visits are needed to complete treatment for skin cancer when using TDS.
- The diagnostic agreement with the clinical and histopathological diagnosis for some diagnoses (including melanoma) is increased by smartphone TDS as compared to paper referrals, while the interobserver concordance is moderate with both methods. With TDS it is easier to plan for surgery at the first visit for patients with skin cancer and more patients with benign lesions can be managed without a FTF visit with a dermatologist. There is a small risk of referrals for malignant lesions to be incorrectly resent to PHC.
- Smartphone TDS images acquired in PHC are not of significantly lower quality than images acquired at a department of dermatology and do not affect the possibility to reach a correct diagnosis.
- The use of DHA can cause new dermoscopic features to temporarily appear in PSLs, especially in facial lesions, in which DHA can cause the lesions to be considered equivocal.

7. Future perspectives

During the time since the studies in this thesis were performed, variants of TDS have been implemented in different regions in Sweden. In Region Västra Götaland, a health technology assessment was performed in 2013, leading to the decision of implementing TDS in the whole region. However, this has proven difficult and it has not been possible to implement an electronic referral such as the one used in study I. Instead, the region has suggested a technological solution (a pilot project started on September 1, 2017) in which only the images are to be transferred electronically while the clinical information regarding the patient and the lesion of concern is sent separately with a traditional paper referral. This means that many of the benefits of the smartphone TDS referral system are lost while others remain.

One of the benefits of smartphone TDS used in study I was that the reply to the referring PHC physician could often be sent after only a few hours (median 1.8 hours), when the case was still current in the referring doctor's mind. This, in combination with the fact that all replies included one or more suggested diagnoses as well as a description of the dermoscopic structures that supported the suggested diagnoses, made each response into an educational opportunity. Studies have shown that PHC physicians who go through structured training in dermoscopy increase their sensitivity for diagnosing melanoma and other skin cancers.[153, 166] However, planning and going through with such training for all PHC physicians in a region or country is likely difficult and time-consuming. If used to its full potential, an electronic referral system could, in combination with lectures introducing PHC to dermoscopy, be important in increasing the skill of dermoscopy in Sweden's PHC. After study I, an online survey was sent out to the 90 PHC physicians for whom e-mail addresses were available and responses were received from 62.2% of those physicians. Out of those that responded, 71.4% found the dermoscopy description to be of great educational value and the remaining 28.6% found that it added some educational benefit.

Adapted versions of the forms used in study II could also be used for such educational purposes. Clinical and dermoscopic images, together with relevant information could be presented, followed by questions testing the participant's diagnostic accuracy in dermoscopy, knowledge about tumour biology and recommended management.

Another potential use of smartphone TDS is patient-controlled, self-monitoring of naevi at a distance. A study protocol is being prepared to investigate this further. Previously, a few pilot studies have found promising results regarding this issue.[269, 270] If found safe, this method could be beneficial

in a number of circumstances. Patients with a few AMLs requiring short-term follow-up, could benefit from digital follow-up from the comfort of their own home, without needing to take time off from work or travel to the dermatology department. For patients with multiple melanomas, or other substantial risk factors, self-monitoring of naevi with smartphone TDS could be added to the current follow-up plan, with the goal of swifter management of new melanomas discovered by the patient. In Sweden, patients with thin melanomas and melanoma in situ are not followed by dermatologists, but over 7% of these patients will develop a second melanoma during their lifetime.[82] The possibility to send dermoscopic images to a dermatologist might lead to these tumours being treated more swiftly. If such a system is implemented, it is of course important not to remove the possibility of performing a TBSE for patients needing this.

The lessons/ideas from study II could also be used to make guidelines for how TDS is used. Of all the 54 triage decisions made for cases of invasive melanoma in the TDS group, only one was incorrect. The evaluating dermatologist considered the lesion to be a pigmented BCC and chose a low priority, which could have meant that the patient would have to wait up to 12 weeks before seeing a dermatologist. Since pigmented BCCs only make up a minority of all BCCs diagnosed in Sweden, it is reasonable to establish a guideline in which all equivocal PSLs are to be given a higher priority. To limit the risk of incorrectly resent referrals, the guidelines could state that all atypical lesions classified as melanocytic by the first step of the two-step algorithm (described in section 1.4.6) should be evaluated FTF. Also, that the option to resend referrals should be chosen based an unequivocal, benign diagnoses rather than in cases where no clear signs of malignancy are seen. Prospective studies could be designed to evaluate the guidelines and how the referral method is used e.g. to detect systematically over- or underprioritised cases.

Although TD/TDS will probably be used most often between PHC and dermatology departments there are other situations where it could also be useful. In especially difficult cases, it could be a way for getting help from other dermatologists i.e. tertiary TD/TDS. It could also be useful for consultations within a hospital, making it possible to get a quick evaluation of patients under the care of other specialists.

Regarding DHA, studies could be planned, to further study if the substance can interfere with dermoscopic evaluations of melanocytic and non-melanocytic skin lesions. One aspect that is not studied is if DHA can hide or mask dermoscopic features (e.g. grey FP in a case of LM/LMM being covered by orange-brown pigment, making the lesions appear more benign). Before using DHA on atypical or malignant lesions, it would be important to consider if it could also interfere with the histopathological evaluation.

When using TDS referrals and monitoring of AMLs with DD, another benefit is that it will be possible to collect a large number of digital images, both clinical and dermoscopic. In many cases a histopathological diagnosis will be available and in others there will be follow-up to make certain the benign nature of the lesion photographed. With such a database of images (that could also include digital, histopathological images) it is possible to train an artificial intelligence that could complement expertise in dermoscopy when evaluating skin lesions with TDS.

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