Development of smartphone apps for skin cancer risk assessment: progress and promise

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Skin cancer is a growing public health problem. Early and accurate detection is important, since prognosis and cost of treatment are highly dependent on cancer stage at detection. However, access to specialized health care professionals is not always straightforward, and population screening programs are unlikely to become implemented. Furthermore, there is a wide margin for improving the efficiency of skin cancer diagnostics. Specifically, the diagnostic accuracy of general practitioners and family physicians in differentiating benign and malignant skin tumors is relatively low. Both access to care and diagnostic accuracy fuel the interest in developing smartphone apps equipped with algorithms for image analyses of suspicious lesions to detect skin cancer. Based on a recent review, seven smartphone apps claim to perform image analysis for skin cancer detection, but as of October 2018, only three seemed to be active. These apps have been criticized in the past due to their lack of diagnostic accuracy. Here, we review the development of the SkinVision smartphone app, which has more than 900,000 users worldwide. The latest version of the SkinVision app (October 2018) has a 95% sensitivity (78% specificity) to detect skin cancer. The current accuracy of the algorithm may warrant the use of this app as an aid by lay users or general practitioners. Nonetheless, for mobile health apps to become broadly accepted, further research is needed on their health impact on the health system and the user population. Ultimately, mobile health apps could become a powerful tool to reduce healthcare costs related to skin cancer management and minimize the morbidity of skin cancer in the population.
RATIONALE FOR USING MHEALTH APPLICATIONS FOR EARLY DETECTION OF SKIN CANCER

There are three main types of skin cancer: malignant melanoma (MM), squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), with the latter two also known as keratinocyte carcinoma (KC). In the last 30 years the incidence of skin cancer adjusted for changes in the age distribution of the population more than doubled in the United States (among Caucasians) and the United Kingdom, nearly doubled in Norway, Sweden, New Zealand and increased by roughly 75% in Australia. For the US it was estimated that about 91,000 people will be diagnosed with melanoma and 9,300 will die due to MM in 2018 and that more than 3 million people received treatment for KCs in 2012. Globally, it was estimated for 2015 that there were about 351,000 new incident melanoma cases and 60,000 melanoma related deaths, with highest burden of disease in Australasia, North America and Europe. This is mostly due to changes in risk factors, such as increased exposure to UV light and indoor tanning. Since these risk factors are mostly preventable, comprehensive prevention programs aiming at better sun-protective behavior have been implemented in several countries, such as SunSmart in Australia.

Although several organizations have issued recommendations on how often to check skin lesions for individuals at higher risk (e.g. Fitzpatrick scale I-III, a family history of melanoma, a history of sun-damaged skin, multiple atypical nevi), ranging from every 3 months to every year, most countries do not have an organized early detection program for skin cancer. The US Preventive Services Task Force has issued an I-recommendation for skin cancer screening, meaning that there is insufficient evidence to evaluate the harms and benefits of skin cancer screening. Currently, there are only two major skin screening programs: (1) in the US, by the American Academy of Dermatology (AAD) which started in 1985, that includes screening and skin cancer awareness education, and (2) in Germany, a national screening program started in 2008. Though, the latter does not seem to be effective in reducing skin cancer related mortality and morbidity.

In practice, it is difficult to provide a high quality skin check even for high risk individuals. A US study found that only a quarter of individuals at higher risk of skin cancer have ever received a total skin body examination. Furthermore, waiting times and, in some areas, dermatologist shortages, out of pocket costs and distance to nearest dermatologist may discourage people at risk from receiving dermatological care. For example, in the US, a study found that availability of a dermatologist within the county is associated with a 35% decrease in melanoma mortality.

In several countries, namely in the United Kingdom and the Netherlands, skin checks are first carried out by a general practitioner (GP, also sometimes referred to as primary care provider [PCP]), whom may then choose to refer a patient to a dermatologist if there is suspicion of skin cancer. However, several studies suggest that the accuracy of GPs to
detect skin cancer is relatively low.\textsuperscript{15-19} The sensitivity of GPs without specific training to detect skin cancer was estimated to be below 60% in a British and a Dutch study.\textsuperscript{15, 16} One US study found that only 35% of patients had a correct diagnosis.\textsuperscript{17} Altogether, this may result in a delay in diagnosis or to miss the cancer in its earlier stages when patient survival is more favorable and treatment is less costly. Furthermore, many GP consultations and/or subsequent referrals to a specialist to examine the skin for cancer result in a benign diagnosis; a Dutch study found that 69% of GP consultations related to suspicious skin lesions result in a benign diagnosis\textsuperscript{19}, and two separate studies in the Netherlands estimated that a large proportion (i.e. 40%) of referred cases to the dermatologist due to suspicion of skin cancer turn out to be benign cases.\textsuperscript{19, 20} Two studies carried out in US and Germany, including in total more than 70 dermatologists, found that dermatologists disease classification decisions have a specificity between 60%-80%, which may result in unnecessary biopsies/excisions.\textsuperscript{21, 22}

Given the preceding, it is believed that early detection and surveillance of skin cancer could become more efficient with Mobile health (hereafter referred to as mHealth) applications which are easily accessible due to the ubiquity of smartphone usage. One example of a smartphone application for self-assessment of skin lesions for skin cancer is the SkinVision application (SVA), developed by SkinVision BV, The Netherlands. In the next section we review the development of the SVA over time.

DEVELOPMENT OF A SMARTPHONE APP FOR SKIN CANCER DETECTION

SkinVision is a smartphone application built as a digital dermatology service for the purpose of self-monitoring skin lesions. It was launched in 2011 and it is currently (October 2018) on its 5th major version. The workflow of the application is given in Figure 1. A user can self-assess the risk of a skin lesion for skin cancer by taking a photo with its smartphone which is processed by an algorithm. The outcome of the procedure is a binary risk rating, which can be low or high. This application does not provide a diagnosis (e.g. “you have melanoma”). For high risk cases, the user receives an advice from the customer care team based on the image assessment of an in-house dermatologist.

Development of the SkinVision application service

The history of the SVA service is shown in Table 1. It went through several upgrades throughout its history affecting the camera, the algorithm and its evaluation, type of lesions analyzed and communication of the algorithm result to its user. One of the major initial challenges was related to the image acquisition. In the beginning there was no filter on the images sent for analyses, which meant that a significant proportion of the pictures
taken by users was of insufficient quality to be analyzed by the disease classification algorithm or didn’t even contain a lesion to be analyzed. Since version 3 of the SVA (2014), a special camera module is embedded which only lets the camera take a photo after certain minimal quality conditions are met. Compared to unfiltered images with standard smartphone camera, the camera module reduces the number of blurry photos by about 52% on average (using 2018 data). Altogether, improvements in the camera module (i.e. image quality checks) and in the algorithm pipeline led to a reduction on the number of assessments that failed to produce a risk rating from 26% in 2016 to 2% in 2018, on average.

An overview of studies on the SVA regarding diagnostic accuracy is shown in Table 2. Diagnostic accuracy is evaluated based on two measures: sensitivity (proportion of correctly classified lesions as high risk) and specificity (is the proportion of correctly rated lesions as benign). The first algorithm for skin lesion assessment was a rule-based fractal algorithm. Initially, it was focused on pigmented skin lesions and only able to analyze whether MM was present in the lesion and it was tested based on clinical review of images. The Munich University Hospital study was the first peer-reviewed publication where the SVA algorithm was evaluated against histopathology; this algorithm scored a 73% sensitivity (83% specificity). During the Catharina Hospital Eindhoven study, the algorithm was recalibrated to
analyze pigmented and non-pigmented lesions. Currently, it can detect several types of skin cancer (MM, SCC and BCC) and skin conditions that can lead to skin cancer, namely, actinic keratosis (AK) and Bowen’s disease (BD). It scored a 80% sensitivity (78% specificity) after inclusion of user clinical information. While in the Eindhoven study only 233 lesions were used for calibration, in 2018 the SVA assembled a training dataset of more than 130,000 images risk classified by a dermatologist from its user database. This led to the replacement of the rule-based classification algorithm by a machine learning approach.

### Table 1. Development of the Smartphone Application.

<table>
<thead>
<tr>
<th>Version</th>
<th>Launch Date</th>
<th>Algorithm</th>
<th>Camera</th>
<th>Type of skin lesion</th>
<th>Type of Skin Cancer Detected</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>May 2011</td>
<td>Rule based fractal algorithm version 1</td>
<td>Standard smartphone camera</td>
<td>Pigmented skin lesion only</td>
<td>MM</td>
<td>Pre-clinical testing using 600 images against the opinion of 2 dermatologists</td>
</tr>
<tr>
<td>2</td>
<td>December 2012</td>
<td>Rule based fractal algorithm version 2</td>
<td>Standard smartphone camera, exclusion criteria introduced</td>
<td>Pigmented skin lesion only</td>
<td>MM</td>
<td>Pre-clinical testing using 600 images against the opinion of 2 dermatologists</td>
</tr>
<tr>
<td>3</td>
<td>September 2014</td>
<td>Rule based fractal algorithm version 2</td>
<td>Camera module: exclusion criteria automated</td>
<td>Pigmented skin lesion only</td>
<td>MM</td>
<td>Clinical Study, Munich University Hospital</td>
</tr>
<tr>
<td>4</td>
<td>July 2016</td>
<td>Rule based fractal algorithm version 3, all outcomes checked by dermatologists (Sept 2016)</td>
<td>Camera module version 1</td>
<td>Pigmented and non-pigmented skin lesions</td>
<td>MM, BCC, SCC, some premalignant lesions</td>
<td>Clinical Study, Catharina Hospital Eindhoven (more types of skin cancer)</td>
</tr>
<tr>
<td>5</td>
<td>January 2018</td>
<td>Machine Learning algorithm for image processing and classification</td>
<td>Camera module major version 2 a</td>
<td>Pigmented and non-pigmented skin lesions</td>
<td>MM, BCC, SCC, some premalignant lesions</td>
<td>Data from previous Clinical Studies and User database with new algorithm</td>
</tr>
</tbody>
</table>

a New features include a dynamic grey threshold to differentiate between normal skin and lesion and a feature that prevents taking pictures without uniform luminosity.

Abbreviations: BCC, basal cell carcinoma; MM, malignant melanoma; SCC, squamous cell carcinoma.
Table 2. Studies on the accuracy of the SkinVision application risk assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Data</th>
<th>Algorithm</th>
<th>Test Set</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maier et al 2014&lt;sup&gt;a&lt;/sup&gt;</td>
<td>University Hospital Munich</td>
<td>Rule-based fractal algorithm version 2</td>
<td>26 lesion with melanoma</td>
<td>73%</td>
<td>83%</td>
<td>Algorithm tested only on MM</td>
</tr>
<tr>
<td>Thissen et al 2017&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Catharina Hospital Eindhoven</td>
<td>Rule-based fractal algorithm version 3</td>
<td>108 lesions including several types of skin cancer</td>
<td>80%</td>
<td>78%</td>
<td>Algorithm tested mostly on KC (Munich data also used for testing)</td>
</tr>
<tr>
<td>Udrea et al 2019&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Clinical Studies and SkinVision application User database</td>
<td>Machine Learning based algorithm</td>
<td>285 lesions with skin cancer, from clinical studies and from user database with histopathology</td>
<td>95%</td>
<td>78%</td>
<td>All types of Skin Cancer</td>
</tr>
</tbody>
</table>

<sup>a</sup> All studies presented here were sponsored by SkinVision BV.
<sup>b</sup> After incorporating answers to a questionnaire about the skin lesion.
<sup>c</sup> Manuscript under peer-review (May 2019). For more details on these results see the Online Supplement.

<sup>Abbreviations: KC, keratinocyte carcinoma; MM, malignant melanoma.</sup>

SkinVision application service in 2018

Camera

Before downloading the app, it is required that the smartphone is equipped with a camera capable of producing a video stream with high enough resolution. While the application uses a regular smartphone camera, the camera module embedded in the application automatically places some restrictions to ensure minimal quality requirements of the images are met: the image needs to be focused, the lesion should be present and contained in the image and there should be no hair or shadows covering the lesion. The module also prevents the camera from taking images which cannot be assessed by the algorithm (e.g. lesions under a nail or in a skin fold, or near clothing).

Algorithm for lesion assessment

There are several steps needed to analyze the lesion. The first task of the algorithm is to identify and separate the lesion from normal skin. This is done using a machine learning technique called conditional Generative Adversarial Neural Network (GAN).<sup>26, 27</sup> After the lesion is segmented, all “noise” (e.g. hair surrounding the lesion) is removed in the image by applying an inpainting procedure.<sup>28</sup> The third step is to extract the features from the lesion which are used in the disease classification algorithm. These features include 24 shape, color and texture attributes that characterize the lesion. A Support Vector Machines (SVM) classifier is used to provide a risk rating, which can be high or low. The SVM
model is obtained by maximizing sensitivity to detect cancer subject to a constraint of a minimal specificity value (e.g. 80%). The optimization is performed using a Particle Swarm Optimization algorithm. The classification algorithm is regularly updated and retrained with new data. This is necessary to maintain robustness to variation due to imaging, newer devices and in the user population adopting the application.

Training and testing
For the training of the algorithm we used images obtained from the user database (more than 130,000 pictures from 30,000 users), which received either a low- or high-risk tag during quality control of the algorithm by a dermatologist affiliated with SkinVision BV. A selection of cases clinically validated as low risk were randomly selected from the user database, while all cases rated as high risk or with histopathological report were used since there are considerably less of them. For testing the sensitivity we used 285 skin lesions (Online Supplement table 1) derived from both the previous clinical studies (Munich and Catharina Hospital, 195 skin lesions, containing most common forms of skin cancer) as well as from the user database (90 cases of melanoma which received histopathological confirmation from users). Furthermore, in order to test the specificity we used 6,000 randomly selected cases from the user database (June-August 2018) tagged as benign by SkinVision affiliated dermatologists and which were not used in training. An overview of these datasets together with the participant flowcharts are shown in Supplementary Information Figures 1-4.

Performance evaluation
The gold standard (main comparator) to evaluate algorithm sensitivity is histopathologically validated cancers. A second comparator is the performance of the algorithm against the image assessment of the dermatologist (which is comparable to a teledermatology consult). In order to calculate the specificity we use images of lesions which were classified by dermatologists as benign cases, since these are not usually biopsied so there is no histopathology report. Sensitivity has improved from 73% in the first peer-reviewed study, where only MM was detectable, to 95% in the current version of the algorithm (78% specificity) where the SVA can detect all forms of skin cancer (Table 2 and Online Supplement).

Post-assessment follow up
Since 2016, images processed by the algorithm are reviewed by at least one affiliated dermatologist. To help users with the interpretation of high risk cases, a senior dermatologist adds advice depending on the probable severity of the disease. The advice can contain the labels “Show”, “Visit” or “Urgent”. “Show” indicates that the lesion should be shown at the next planned doctor appointment, “Visit” indicates that the appointment should
be made soon and “Urgent” advises the user to show the lesion to a doctor as soon as possible. Users with a low-risk rating only receive a reminder to check their skin regularly. Assessments with a high risk rating given by the dermatologist are followed up by the customer support department of SkinVision. If the user does not respond he/she may receive additional messages encouraging a visit to the doctor depending on the perceived severity of the disease. Some users share their diagnosis of skin cancer with SkinVision (n=3,806, see Supplementary Figure 3). Out of these, a small proportion (8.8%, n=338/3,806) share the histopathology report. At the end of September 2018, about 338 users have shared histopathological reports of which 58% (178/338) were MM. The histopathological validated cases are used for training and testing the algorithm.

SMARTPHONE APPLICATION USERS

In Table 3, we show self-reported demographic data on SVA users. As of September of 2018, the SVA has performed more than 1.8 million assessments. Some of these users shared their demographic data with SkinVision: 56% (355,491 out of 635,807) shared their age group and 28.5% (181,706 out of 635,807) their gender. Although skin cancer is more prevalent in older age groups, there are few people older than 60 (7%, 19,358 out of 355,491) in the user database. One third (31%, 110,529 out of 355,491) of the users sharing their age is younger than 30 years old. More than 60% of the users are female (118,182 out of 181,706). The majority of users come from the following countries: The Netherlands (111,063 users, 17.4%), United Kingdom (109,178 users, 17.2%), Australia (109,126 users, 17.2%), New Zealand (70,244 users, 11%) and Belgium (21,328 users, 3.3%).

STATE OF THE FIELD

Available mHealth applications for skin cancer detection

In a recent review it was found that there are 43 smartphone applications developed for skin cancer detection, monitoring or education. Of these, it is claimed that nine smartphone applications use an algorithm for image analysis. We verified the current status of these applications in December 2018 with Google search, Pubmed and in app stores. Results are presented in Table 4. We confirm that seven applications claim to use an algorithm for image analysis. Of these, four do not seem to be active anymore. Compared to a previous review carried out in July 2014, there are now less applications available for risk assessment of skin lesions through image analysis (3 instead of 4).
Comparison of SkinVision application with other applications

Currently, there seem to be three smartphone applications available for detection of skin cancer, including SkinVision, Spotmole and skinscan. All three allow the user to take a picture with the smartphone camera. The SkinVision application algorithm is based on machine learning techniques while Spotmole and skinscan use algorithms inspired in the ABCDE rule.\textsuperscript{33} Whereas the SVA has a quality control provided by a dermatologist, other apps do not seem to offer any further follow-up or advice to users.

In Tables 2 and 5, results regarding the diagnostic accuracy from recent publications are shown. We found 5 peer-reviewed studies and one submitted study about 2 available applications (SkinVision and Spotmole) concerning skin cancer, and 2 applications which do not exist anymore. No studies on diagnostic accuracy (or other studies) were found for the

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**Table 3.** Self-reported demographic characteristics of the users of the SkinVision application \textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Registered Users</td>
<td>931 789</td>
</tr>
<tr>
<td>Total Number of Users with an assessment</td>
<td>635 807 \textsuperscript{b}</td>
</tr>
<tr>
<td>Gender, n (%) \textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 914 (9.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>118 182 (18.6%)</td>
</tr>
<tr>
<td>Missing</td>
<td>454 731 (71.5%)</td>
</tr>
<tr>
<td>Age, n (%) \textsuperscript{c}</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>110 529 (17.4%)</td>
</tr>
<tr>
<td>30-39</td>
<td>98 327 (15.5%)</td>
</tr>
<tr>
<td>40-49</td>
<td>74 928 (11.8%)</td>
</tr>
<tr>
<td>50-59</td>
<td>46 840 (7.4%)</td>
</tr>
<tr>
<td>60-69</td>
<td>19 358 (3.0%)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>5 509 (0.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>280 316 (44.0%)</td>
</tr>
<tr>
<td>Country of residence, n (%)</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>111 063 (17.4%)</td>
</tr>
<tr>
<td>Australia</td>
<td>109 178 (17.2%)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>109 126 (17.2%)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>70 244 (11.0%)</td>
</tr>
<tr>
<td>Belgium</td>
<td>21 128 (3.3%)</td>
</tr>
<tr>
<td>Others</td>
<td>215 355 (33.9%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The data is obtained from the SkinVision application proprietary user database, accessed in September 2018. Numbers are based on users who made a picture that was evaluated by the algorithm and who completed the online questionnaire.

\textsuperscript{b} As some users may be healthcare providers taking pictures of multiple patients using the same user account, this is likely to be an underestimate.

\textsuperscript{c} For the gender and age categories about 75% and 44% respectively did not fill any data.
Table 4. List of smartphone applications that claim to do skin lesion image analyses to detect skin cancer, based on the systematic review of Ngoo et al. 2018

<table>
<thead>
<tr>
<th>Commercial Name</th>
<th>Algorithm</th>
<th>Evidence on PubMed</th>
<th>Status</th>
<th>Link to Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DermaCompare</td>
<td>Machine Learning</td>
<td>Not found</td>
<td>Removed from app store, last update January 2017</td>
<td>appadvice.com/app/derma-compare/982517772</td>
</tr>
<tr>
<td>Lubax</td>
<td>Content based imaged retrieval, k-nearest neighbor</td>
<td>One supported peer-reviewed publication</td>
<td>Removed from app store, last update February 2015</td>
<td>appadvice.com/app/lubax-skin-lesion-id-using-image-recognition/956423382</td>
</tr>
<tr>
<td>MSkinDoctor</td>
<td>Grab cut algorithm (segmentation) and SVM (classification)</td>
<td>Not found; there is a conference abstract only</td>
<td>Removed from app store, update February 2016</td>
<td><a href="http://www.appbrain.com/app/mskin-doctor/com.maleemtaufiq.mSkinDoctor">www.appbrain.com/app/mskin-doctor/com.maleemtaufiq.mSkinDoctor</a></td>
</tr>
<tr>
<td>MySkinMap</td>
<td>Machine Learning</td>
<td>Not found</td>
<td>Removed from app store, last update September 2016</td>
<td>appadvice.com/app/myskinmap/1151655127</td>
</tr>
<tr>
<td>skinscan</td>
<td>Image processing techniques, ABCDE rule</td>
<td>Unclear</td>
<td>Available</td>
<td>Teleskin.com appadvice.com/app/skinscan/1025190936</td>
</tr>
<tr>
<td>SkinVision</td>
<td>conditional Generative Adversarial Neural Network (segmentation) and SVM (classification)</td>
<td>Two supported peer-reviewed publications, evaluated in independent publications</td>
<td>Available</td>
<td><a href="http://www.skinvision.com">www.skinvision.com</a> 23-26</td>
</tr>
</tbody>
</table>

* After verifying the websites of every application (if available), it seems two of the applications mentioned by Ngoo et al. 30 with the commercial names Myskinpal and Skin Prevention – Photo Body do not claim to perform automated image analyses for risk assessment. They merely store images of moles to track changes.

* If available, information is retrieved from scientific publications, otherwise from the companies own website or app store description.


* There is an associated reference to an application of the same name from 2011. However, this does not appear to be the same application.

* Results obtained in this publication only for melanomas and large lesions. 32

* There is another application available with the same name, however that one does not perform image analyses.

* This smartphone application has a website (www.spotmole.com). However, it is at the last time of access, 12/12/2018, offline. It is doubtful if this project is still alive, given the fact that the last update was in March 2016, and that it seems this application is being developed by a single individual.

Abbreviations: SVM, Support Vector Machines.
skinscan application. The other two smartphone applications (SkinVision and Spotmole) were evaluated in at least one study, and only one application (i.e. SkinVision) has published evidence to show whether their proprietary algorithm is accurate.

mHealth applications for skin cancer assessment (including the SVA) have been criticized in past studies since their accuracy was found to be significantly lower than a dermatologist. In Tables 2 and 5, only three studies show a diagnostic accuracy near that of a dermatologist and one of these did only show a high accuracy for large melanoma lesions. Even though some of these studies are recent, these findings are possibly already outdated as this is a rapidly evolving field. These results could also be explained by the

Table 5. Recent studies on the diagnostic accuracy of smartphone applications for risk assessment of skin lesions.

<table>
<thead>
<tr>
<th>App Study</th>
<th>Data</th>
<th>Algorithm</th>
<th>Test Set</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SkinVision application</td>
<td>Princess Alexandra Hospital, Brisbane,</td>
<td>Rule based fractal algorithm version 2</td>
<td>1 MM, 41 clinically suspicious lesions</td>
<td>iOS 57% (41-73)</td>
<td>iOS 50% (22-78)</td>
<td>Only 1 MM was found</td>
</tr>
<tr>
<td>Ngoo et al 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spotmole</td>
<td>Princess Alexandra Hospital, Brisbane,</td>
<td>Algorithm based on ABCDE rule</td>
<td>1 MM, 41 clinically suspicious lesions</td>
<td>43% (28-58)</td>
<td>80% (60-100)</td>
<td>Only 1 MM was found</td>
</tr>
<tr>
<td>Ngoo et al 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr. Mole</td>
<td>Princess Alexandra Hospital, Brisbane</td>
<td>Algorithm based on ABCDE rule</td>
<td>1 MM, 41 clinically suspicious lesions</td>
<td>21% (9-34)</td>
<td>100% (100-100)</td>
<td>Only 1 MM was found</td>
</tr>
<tr>
<td>Ngoo et al 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubax</td>
<td>DermNetZN and Los Angeles</td>
<td>Content Based Image Retrieval</td>
<td>208 lesions with melanoma</td>
<td>90% (86-94)</td>
<td>92% (85-95)</td>
<td>Algorithm tested only on MM (large lesions only)</td>
</tr>
<tr>
<td>Chen et al 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Reported</td>
<td>Galway University Hospital</td>
<td>Not reported</td>
<td>9 MM</td>
<td>80% (52-96)</td>
<td>9% (0-41)</td>
<td>Algorithm tested only on MM</td>
</tr>
<tr>
<td>Dorairaj et al 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a Ngoo et al. reported the results per type of operating system: iOS/Android. The above confidence interval is for iOS.

*b All lesions had a benign final histopathology diagnosis with the exception of 1 melanoma in situ.

c DermNetZN is a publicly accessible skin lesion image database from New Zealand containing about 20,000 images. Link: https://www.dermnetnz.org/. Last access on 15 April 2019. Images collected within the Los Angeles county were collected by the application’s company. No reference to a clinical site of the data collection was given in the publication.

d Algorithm was only tested on “large lesions” defined as melanomas with a diameter equal or larger than 10 mm.

e Despite the study being published in 2017, the study took place in 2012.

Abbreviations: MM, malignant melanoma.
limited sample size including too few skin cancer cases and selected samples, which may be inadequate to calculate sensitivity and/or specificity or in the case of the SVA not utilizing the full service with the dermatologist advice.

Overall, the amount of evidence on the diagnostic accuracy of smartphone applications is still scarce as there are few mHealth applications providing this service. It is also difficult to make an accurate comparison between different applications, since the rate of service or algorithm change is generally faster than the process of peer-review publication. It could also be the case that some developers may choose to publish their results in sources which are not referenced in PubMed, namely on ArXiv. An illustrative example of these difficulties is a Cochrane review published in December 2018 on the diagnostic accuracy of smartphone applications, which only found two studies but only included articles published before August 2016, making it possibly obsolete at the time of publication. For these reasons, one should be cautious when interpreting available literature.

**Improving diagnostic accuracy of mHealth applications**

A promising avenue to improve diagnostic accuracy of mHealth applications is to train machine learning algorithms on large databases of skin cancer images. Several algorithms for skin cancer classification were recently developed based on clinical or dermoscopic images, with algorithm accuracy routinely on par with a dermatologist. For mHealth applications, the task of skin lesion classification is more difficult, as the images are taken by the users themselves, with variability in angle, luminosity and smartphone model. The SVA showed that skin lesion classification based on smartphone images can also achieve high accuracy (Table 2).

**ALTERNATIVES TO MHEALTH APPLICATIONS**

Early detection of skin cancer could be significantly improved by launching a population screening program, but this is unlikely to become common given the high costs and lack of evidence on harms and benefits. As the main risk factors for skin cancer like indoor tanning or UV exposure are in large part preventable, primary prevention and awareness campaigns (e.g. Melanoma Monday, SunSmart in Australia) could have a better cost benefit ratio compared to early detection. These campaigns are a way for the general public to proactively adopt preventive behaviors and possibly learn how to recognize suspicious skin lesions and seemed to have resulted in better sun-protection behaviour. On the other hand, this success can be reversed if these awareness efforts are not continuous and they do not solve the shortages or difficulties in access to high quality skin checks.

Training GPs or nurses with a special interest to recognize skin cancer increases the capacity for early and accurate detection. However, compared to mHealth applications,
it still requires face-to-face contact and it is also likely not enough to address all needs of patients.\textsuperscript{13, 42} Store-and-forward teledermatology allows users to take a photo and get it analyzed remotely by a dermatologist.\textsuperscript{43} This may solve some of the problems with access to care, but is solely based on a clinical assessment of a healthcare professional and is thus not automated. Good performing smartphone applications are likely to be more efficient and could lead to larger cost savings for the health system compared to the above mentioned alternatives.

**USABILITY RISKS OF MHEALTH APPLICATIONS**

Smartphone applications pose some risks for the user. First, if the algorithm returns a negative result while the user has cancer (i.e. false negative) and detection and treatment of skin cancer is delayed. It is very challenging to study the rate of false negatives due to lack of histological verification of assumed benign lesions. Second, the user may also fail to assess all relevant skin lesions, in particular if they are located in places which are hard to reach or which the user cannot see. Third, given that the specificity of the SVA is about 80%, there will be a few false positive cases. This may cause unnecessary stress on users and/or unnecessary visits to the GP/dermatologist. Finally, the user may not follow the advice given in the SA due to lack of trust or unawareness.

**EVALUATING THE HEALTH IMPACT OF MHEALTH APPLICATIONS**

**Impact of mHealth applications on healthcare costs**

A Dutch study based on national claims data observed an increase by about 67% of skin cancer related costs between 2007 and 2017.\textsuperscript{44} This is due to higher costs of skin cancer treatment, for example due to newly available expensive targeted- and immunotherapies for late stage melanomas, and to a lesser extent due to a rise in skin cancer incidence. Smartphone applications for self-assessment of skin lesions could limit this cost increase in two ways: (1) by detecting cancers early, which will reduce the average cost of treatment and recovery due to the disease being less advanced, and (2) by reducing the need for doctor visits since many GP consultations may either result in a benign diagnosis or in referrals to a specialist of cases that are later diagnosed as benign.\textsuperscript{19}

**Impact of mHealth applications on public health**

Easy access to a high quality assessment of skin lesions may lead to detection of skin cancers at an earlier stage when their prognosis and treatment are more favorable. On the other hand, this may also cause over diagnosis and overtreatment. Currently, the evidence
on the benefits and harms of skin cancer screening is insufficient. To date, there are no randomized skin cancer screening trials, and it is unlikely that there will be new trials launched in the near future since they would require a substantial number of patients, a long follow up, and it would be difficult and possibly unethical to guarantee that people in the control group would not access skin cancer detection methods. Consequently, it is difficult to show whether or not early detection of skin cancer reduces skin cancer specific mortality. Another important target outcome could be the incidence of advanced melanoma. Therefore, indirect evidence on harms and benefits could be obtained by comparing the stage distribution of cancers detected early with a SA with cancers in national registries.

**Implementation of mHealth applications in the health system**

The health impact of mHealth applications also depends on where it is implemented, i.e. restricted to healthcare professionals such as GPs or dermatologists or accessible to the lay population. Offering applications directly to lay users could result in significantly greater efficiency gains for the health system. However, some regulatory bodies may prefer to restrict the usage to healthcare professionals with the goal of minimizing usability risks. The regulatory framework is evolving quickly, with NICE in the United Kingdom suggesting a comprehensive approach to regulate mHealth technologies taking into account not only the safety and efficacy of the application, which can be shown by carrying out a diagnostic accuracy study, but also whether it can plausibly improve current healthcare pathways, acceptability with users and finally its cost-effectiveness compared to usual care.

**Barriers to access of mHealth applications**

After implementation, the health impact of mHealth applications will also depend on the persistence of barriers to adoption among users (either lay persons or care providers). Zhao et al have described a technology acceptance model for mobile health. For lay users, age can play a role in the rate of adoption. Middle age and older users (the ones who are at higher risk of skin cancer) may give more importance to the perceived amount of effort needed to learn how to use the smartphone application and the perceived personal risk for skin cancer. For clinicians, we believe the perceived ease of use also plays an important role since clinicians have a limited amount of time. Other important factors may include, perceived usefulness and efficacy of the smartphone application, namely, whether clinicians believe in the quality of the smartphone application, and whether they believe it provides the necessary information to make a clinical decision.

**Post-market surveillance of mHealth applications**

A key point for mHealth applications for skin cancer detection consists of taking appropriate market surveillance activities in order to minimize usability risks, since data based
on clinical studies in a controlled setting is likely not sufficient to control for differences in image taking behavior or in the characteristics of the smartphone model. Algorithms used in smartphone applications should then be updated periodically given the feedback from its users, whether they are lay users or clinicians. It is not easy to have complete follow up from users since due to privacy reasons it is not straightforward for smartphone applications to get access to the final clinical or histopathological diagnosis after the lesion is assessed by the algorithm.

**FUTURE RESEARCH**

Research is still needed to establish the societal value of mHealth. First, there remains a need for more high quality studies on their diagnostic accuracy in different populations. Second, given that these smartphone applications are accurate enough to be used by laypersons and GPs, its health and cost effects are yet to be evaluated.

The impact on the health system in terms of cost reduction due to less skin lesion related visits still needs to be tested, ideally with a randomized control trial (RCT) accompanied by a cost-effectiveness analysis. However, performing an RCT may prove difficult. For the goal of designing a trial capable of detecting a difference in the number of doctor visits, Dutch data from 2010 suggests that about 93 consultations in every 1,000 patients are related to skin cancer, and therefore the sample size needed to carry out such a study is in the thousands of patients. The main problem is that this sort of RCT has a high risk of contamination in the control group (no smartphone application use), since access to smartphone applications and their usage are relatively simple. An alternative solution could be to follow a quasi-experimental approach for the design of the study.

In the absence of large RCTs and/or long term follow-up data, modelling could be used to estimate the harms and benefits of early detection of skin cancer. There are a few studies in the literature which modelled the incidence and mortality of skin cancer. The main drawback of these modelling studies is the difficulty in estimating tumor onset and progression. This could be addressed by forming a coalition of multiple modelling groups for skin cancer, like the Cancer Intervention and Surveillance Modelling Network (CISNET) group has done for other cancer sites.

**SUMMARY AND CONCLUSIONS**

Given the difficulties in access to high quality care for early detection for skin cancer, there is considerable interest in developing algorithms and applications for skin cancer lesion assessment. Although smartphone applications have been criticized in the past due to
poor accuracy, the SVA has a high accuracy to evaluate the risk of skin lesions for skin cancer. This was achieved thanks to improvements in the processing of images taken with the smartphone camera and a large risk labeled image database from users which was used to train a machine learning algorithm.

However, there are still many open questions regarding the usage of mHealth applications. National health authorities need to decide where to position these applications in the health care system (lay population, GPs, dermatologists). Health effects of early and more accurate detection are hard to estimate. There is currently no high quality evidence on the health and cost benefits and harms of early detection of skin cancer, namely on the trade-off between doctor visits and lives saved/advanced cases avoided. The reduction of the skin cancer burden on the health system and in the population could be substantial, as earlier detection of skin cancer could result in a lower average cost of treatment and in a reduction of doctor visits. However, further studies are needed to confirm this.
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