
JMIR Dermatology

All topics related to diseases of the skin, hair, and nails, with special emphasis on technologies for information exchange, education, and clinical care

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Original Paper

Participation in Clinical Trials Among Academic Dermatologists Affiliated With Veterans Affairs Hospitals: Survey Study

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Abstract

Background: Clinical trials have led to the development of new and effective therapies for many dermatologic conditions. To our knowledge, there is no published study that has quantified and described the degree of involvement in clinical trials among academic dermatologists and their university affiliates.

Objective: The purpose of this study was to characterize the involvement of academic dermatology departments in clinical trials research.

Methods: An online survey was sent to 211 Veterans Affairs (VA)-employed dermatologists. It comprised 20 questions related to the number of clinical trials, support staff dedicated to clinical research, skin diseases studied, and the effect of the COVID-19 pandemic on conducting clinical research. Three rounds of survey invitations were sent over a 3-month period (March to May 2021). Data from all survey responses were reviewed for quantitative and descriptive analyses of the key outcome measures.

Results: A total of 48 dermatologists completed the survey and provided their university affiliations and details of involvement in clinical trials research. Over half of participants (n=25, 58.1%) with a university affiliate reported that their affiliated dermatology department had a dedicated clinical trials unit. Basal cell carcinoma was the most frequently studied skin condition (n=9, 18.8%), followed by atopic dermatitis and psoriasis (n=4, 8.3% each); 66.7% of participants reported no current clinical trials participation. Of those conducting clinical trials, 87% (n=18) noted that COVID-19 was a barrier to conducting trials, with 52.2% (n=11) citing disrupted or decreased trials due to the pandemic.

Conclusions: Although many dermatologists with university affiliations reported having a dedicated clinical trials unit at their institution, a majority of those surveyed reported not taking part in any active trials. Overall, the diseases investigated in academic clinical trials appear to follow national trends, though some of the top dermatological diseases are underrepresented in clinical trials research. A key limitation of our study was the low response rate (~23%) and that the survey responses from the sample of VA-based dermatologists may not be generalizable to all academic dermatology departments in the United States. The effect of the COVID-19 pandemic appeared to play a significant role in disrupting active trials.

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KEYWORDS

dermatology; dermatologists; clinical trial; COVID-19; basal cell carcinoma; psoriasis, atopic dermatitis; Veterans Affairs; carcinoma; cancer therapy; dermatologist; pandemic

Introduction

Skin conditions are a common and burdensome health problem in the United States, with 1 in 3 people affected at a given time [1]. These conditions are associated with negative emotional effects and a reduced quality of life, which contribute to increased direct and indirect medical costs [1], and underscore the importance of establishing efficacious treatment options. Recent advances in our understanding of dermatologic diseases have enabled the development of cutting-edge drugs and procedures. At the forefront of these developments are clinical trials, with common skin diseases such as psoriasis and atopic dermatitis well represented in clinical trials research [2]

A clinical trial, as defined by the International Committee of Medical Journal Editors, is research that prospectively assigns human participants to intervention and concurrent comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome [3]. Clinical trials test treatment efficacy, advance our knowledge of medical procedures, and may offer access to more beneficial drugs compared to standard therapeutic options.

Although clinical trials are essential for the advancement of contemporary medicine and the field of dermatology, clinical trials research among Veterans Affairs (VA)-affiliated academic dermatology departments and their associated institutions reportedly varies by type and degree of participation [1]. To our knowledge, there have been no studies characterizing the degree to which academic dermatology departments are involved in clinical trials, nor any that address which dermatologic conditions are most frequently studied and which are currently underrepresented in clinical trials. We sought to characterize the involvement of academic dermatology departments in clinical trials research with respect to the institutional support provided for clinical trials, the conditions studied, availability of research support, and barriers to conducting clinical research.

Methods

Overview

An online survey was created via SurveyMonkey (Momentive Inc) (see [Multimedia Appendix 1](#) for complete survey questions and response summary) and was piloted among local VA dermatologists, who provided feedback and contributed to the final survey design. The final survey consisted of 20 questions asking for information related to the number of clinical trials, support staff dedicated to clinical research, skin diseases studied, and the effect of the COVID-19 pandemic on conducting clinical research. VA-based dermatologists were identified by a listserve

and invited to participate in an online survey-based assessment. Three rounds of survey invitations were sent over a 3-month period (March to May 2021), with 211 potential participants contacted via email and invited to participate.

Data from all survey responses were reviewed for quantitative and descriptive analyses of the key outcome measures. Two reviewers (MK and TK) independently tabulated survey responses, and a third reviewer (TS) confirmed the results.

Ethical Considerations

The study was granted an exemption by the Colorado Multi-Institutional Review Board and was approved by the VA Eastern Colorado Health Care System Subcommittee on Research Safety.

Results

A total of 48 VA dermatologists (48/211, 22.7%) completed the survey. Responses are summarized in [Multimedia Appendix 1](#). All dermatologists who were surveyed reported having active VA appointments and currently seeing patients, with 16 (33.3%) reporting participation in clinical trials research. More than half of all respondents (n=31, 66%) reported not currently studying any dermatologic conditions, although 38.7% (12/31) of these reported prior (n=6) or planned (n=7) clinical trials research (includes 1 participant who reported both prior and planned research). The majority (n=43, 89.6%) reported an affiliation with the dermatology department of a university; 25 (58.1%) reported their university's dermatology department had a dedicated clinical trials unit.

Among the dermatologic conditions currently being investigated in clinical trials, basal cell carcinoma was the most frequently studied (participants: n=9, 18.8%; institutions: 26.7%), followed by atopic dermatitis and psoriasis (participants: tied at n=4, 8.3%; institutions: 10.0%). Of survey participants, 39.6% (n=19) reported no involvement in clinical trials. Lack of time (n=29, 60.4%) and lack of resources (n=30, 62.5%) were cited most frequently as barriers to involvement in clinical trials research. For those who reported active participation in clinical trials, most were involved in 1 or 2 trials (n=6, 12.5% each; total: n=12, 25%). Among those who reported participation in clinical trials research, 52.2% noted an interruption or decline in clinical trials research secondary to the COVID-19 pandemic; 13% cited lack of time due to increased clinical and administrative duties, and another 8.7% were unable to recruit adequate numbers of staff or new patients. The remaining 13% stated that COVID-19 had a limited effect on their ability to conduct clinical trials. Comments describing the impact of COVID-19 on clinical research appear in [Textbox 1](#).

Textbox 1. Additional comments regarding the effect of COVID-19 on clinical trials research. VA: Veterans Affairs.

1. "Both University and VA were designated COVID hospitals. The U. is live again; the VA is evaluating studies on a case by case basis. None reopened yet."
2. "Cancelled one trial - very limited support from the VA - will be leaving the VA soon due to lack of support for research"
3. "Clinical trial placed on hold and could not enroll. When we could enroll, patient no longer qualified"
4. "Continued to do studies with established patients. Couldn't start new trials or enroll new patients for a while"
5. "Currently not actively engaged in projects; however, have been limited in the number of patients able to be seen, and projects, in general, have been placed on hold."
6. "Decreased activity severely"
7. "Delays"
8. "Fewer clinical trials"
9. "For the VA in particular, key staff were limited in terms of availability and responsiveness. For the university affiliate, there was nearly a month delay in IRB review/approvals related to holiday closure and longer time off for staff (related to COVID surge)"
10. "Had to pause one clinical trial, yet two are epidemiologic studies for which we are struggling to find statistical support"
11. "Hard to keep up with clinical duties"
12. "Have not been able to do research"
13. "I have had to focus on clinical and administrative work (vs science) almost exclusively since COVID."
14. "Lab and trials were shut down for many months and now only partially active"
15. "Limited recruitment for a period of time"
16. "Lack of access to patients, and money/resources"
17. "Limited effect"
18. "COVID-19 has not affected my trials."
19. "Patient numbers at our institution are severely limited. Would make doing research very challenging, since we can't get all our veterans with active problems seen in a timely fashion"
20. "Slowed it"
21. "Trials put on hold. Trial coordinator working virtually."
22. "VA staff who participate are focused on COVID response and don't prioritize participation in research"
23. "Only doing clinic now"

Discussion

Principal Findings

Our study revealed that basal cell carcinoma was the most frequently studied skin problem among VA dermatologists, likely correlating to the high incidence of skin cancer in the VA population [4]. Psoriasis and atopic dermatitis were the second most commonly studied conditions. This is in line with other recent work [5] that suggests an ongoing trend of psoriasis and atopic dermatitis being among the most researched skin conditions. Assessment of the clinical trials database maintained by the US National Library of Medicine [6] as of July 22, 2021, similarly reflects the prominence of psoriasis and atopic dermatitis among dermatologic trials, demonstrating that, for the conditions reported in our survey, psoriasis accounts for the greatest number of active trials (n=727) nationwide, followed by atopic dermatitis (n=450 active trials) and basal cell carcinoma (n=176 active trials).

A comparison of the conditions reported in this study to epidemiological data (1990-2017) from the Global Burden of Disease study [7] and its disability-adjusted life-year estimates

for the most burdensome dermatological conditions in the United States [8] shows that several top skin diseases (including acne, alopecia areata, contact dermatitis, urticaria, and viral and fungal skin diseases) were not investigated by any of the survey respondents in our study. However, this could be due to the small sample size and low response rate failing to capture all diseases being studied by academic dermatology departments in clinical trials.

In addition to gauging involvement in clinical trials among VA dermatologists and their associated academic institutions, this study sought to understand the impact of COVID-19 on participation in clinical trials. Though survey participants reported lack of time and resources as the greatest barriers overall to pursuing clinical trials research, COVID-19 was noted to pose new challenges such as disruptions and delays in trials, lack of access to patients and resources, and increased clinical obligations. Other studies have likewise found the pandemic poses many obstacles for clinical researchers and study participants, including, but not limited to, site closures, mandatory self-isolation, travel restrictions, interrupted delivery of investigational products, infection of staff or study

participants, significant delays in the enrollment of subjects, and difficulty in study monitoring [9,10].

Limitations

Limitations of this study include a low survey response rate (~23%) and inclusion of only VA-affiliated dermatologists. We estimate that the listserv used to distribute surveys may have missed approximately 46 VA-affiliated dermatologists who would have been eligible to participate; inclusion of these dermatologists would increase the denominator and further decrease the survey response rate.

Conclusion

Our study suggests that academic dermatology departments are conducting clinical trials in line with current national trends, with atopic dermatitis and psoriasis at the forefront of clinical

trial efforts. It remains a challenge to balance patient care and clinical research missions within academic dermatology departments. Additionally, securing adequate support in the form of qualified study personnel and financial resources support to conduct high-quality research can be a barrier to maintaining clinical trials units, especially during the COVID-19 pandemic. Further work should be done to survey academic dermatology departments directly and to compare the results with published trials on ClinicalTrials.gov. Use of the ClinicalTrials.gov database could also include surveying the full list of dermatology-related clinical trials site locations to see which of these are affiliated with academic institutions. Such studies would provide a more robust assessment of investment in clinical trials research among teaching hospitals and dermatology faculties.

Conflicts of Interest

RD is editor-in-chief of *JMIR Dermatology*, a joint coordinating editor for *Cochrane Skin*, a dermatology section editor for UpToDate, a social media editor for the *Journal of the American Academy of Dermatology* (JAAD), and a podcast editor for the *Journal of Investigative Dermatology* (JID). He is a coordinating editor representative on Cochrane Council. TS is an editorial board member-at-large for *JMIR Dermatology*.

RD receives editorial stipends (JAAD, JID), royalties (UpToDate), and expense reimbursement from *Cochrane Skin*. TS receives fellowship funding from Pfizer and the National Institutes of Health (grant 2T32AR00741136A1; principal investigator: Dennis Roop).

Multimedia Appendix 1

Survey with response summary.

[DOCX File, 19 KB - [derma_v5i3e35379_app1.docx](#)]

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Abbreviations

VA: Veterans Affairs

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Research Letter

Piloting a Community Education Skin Cancer Program Coordinated by Medical Students

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skin cancer; skin; cancer; oncology; dermatology; community education; health education; pediatric; paediatric; skin of color; sun exposure; tanning; service; child; school age; school; student; medical student; health literacy; telehealth; teledermatology; telemedicine; online education; distance education; internet-based; digital health; melanoma; patient education; prevention

Skin cancer is the most common cancer in the United States with a dramatic increase in the risk of melanoma development after serious sunburn [1]. The United States Preventative Service Task Force recommends that all children and young adults aged 6 months to 24 years be counseled about skin cancer prevention and sun protective habits [2]. Block the Blaze (BTB) is a nonprofit run through the John Wayne Cancer Foundation (JWCF) that is dedicated to educating school-age students about skin cancer detection and sun-protective habits. The Mayo Clinic Alix School of Medicine (MCASOM) is one of the few medical school chapters of the nonprofit, highlighting opportunities for increased medical student community engagement. All volunteers were required to complete both the Melanoma Research Foundation's melanoma educator certification course and virtual training held by the JWCF on presenting to school-age children in the community. Community presentations focus on teaching school-age children about sun-protective habits, skin cancer risk factors, and completing thorough skin checks. The goal of the MCASOM BTB community education program is to reach as many students as possible virtually while working to transition to a hybrid virtual and in-person format and expanding within the Rochester Public School District.

The leadership structure for BTB at MCASOM consists of an internal team that coordinates volunteers and an external team that coordinates community outreach for presentations. Presentations can only be scheduled during the high school, middle school, and elementary school academic calendar from September to May.

Although leadership for BTB consisted of students from Mayo Clinic campuses in Arizona and Minnesota in the first half of its term, the 2 volunteer groups began to run autonomously in the second half of its term in anticipation of in-person community presentations as the pandemic subsided. The timelines of the first and second terms are visualized in [Figures 1 and 2](#).

Modifications to the curriculum provided by the JWCF included updating California skin cancer statistics to those of the local state. Images were also updated to include more skin of color. Photographs of dermatological conditions on skin of color are limited and variable at the national level [3], which in turn can be contributing to survival rate disparities and delayed diagnosis of melanoma in people of color [4].

A total of 113 teachers were contacted in Minnesota during the first term across different middle and high schools. The response rate to external emails was around 3.5%. A total of 40 presentations were scheduled, and 424 students were reached at local schools, representing more than 2.4% (424/17,474) of Olmsted County's student population. The virtual programming facilitates greater geographic reach for contacted schools and provides scheduling flexibility so that volunteers from other campuses could cover presentation shifts in a different state when needed. However, the drawbacks of the virtual format include technical and connection problems, lack of audience feedback, and difficulties in coordinating with schools that are having in-person classes. Community engagement interventions

are often used to improve public health awareness and education, disadvantaged groups [5]. address health care disparities, and offer social support for

Figure 1. Framework, timeline, and results of the first half of year 1 (spring). AZ: Arizona, MN: Minnesota.

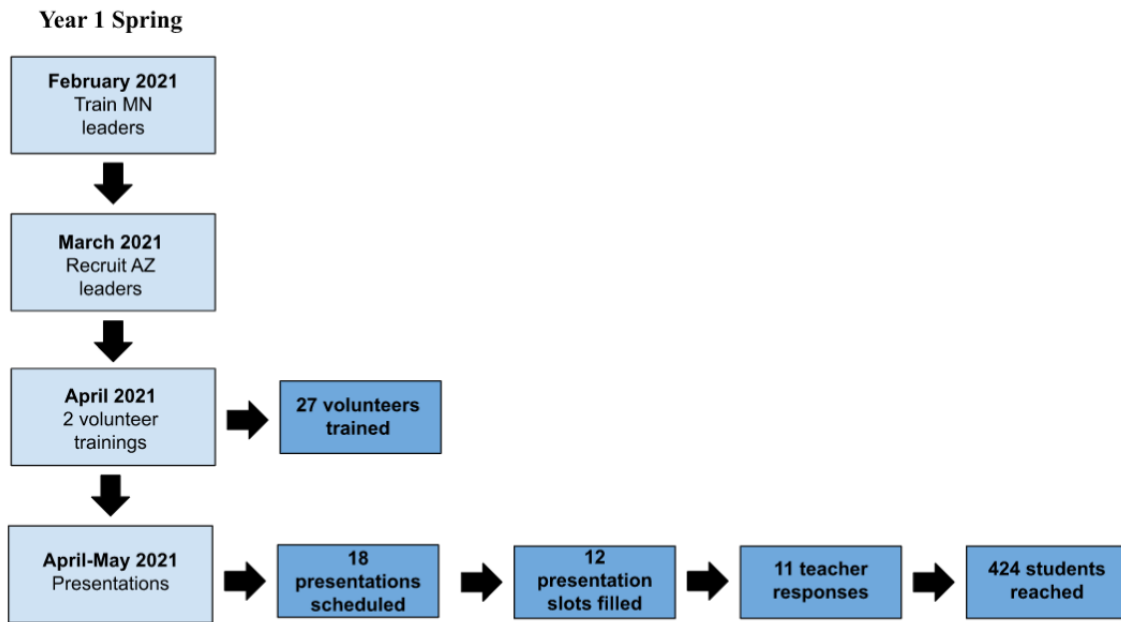
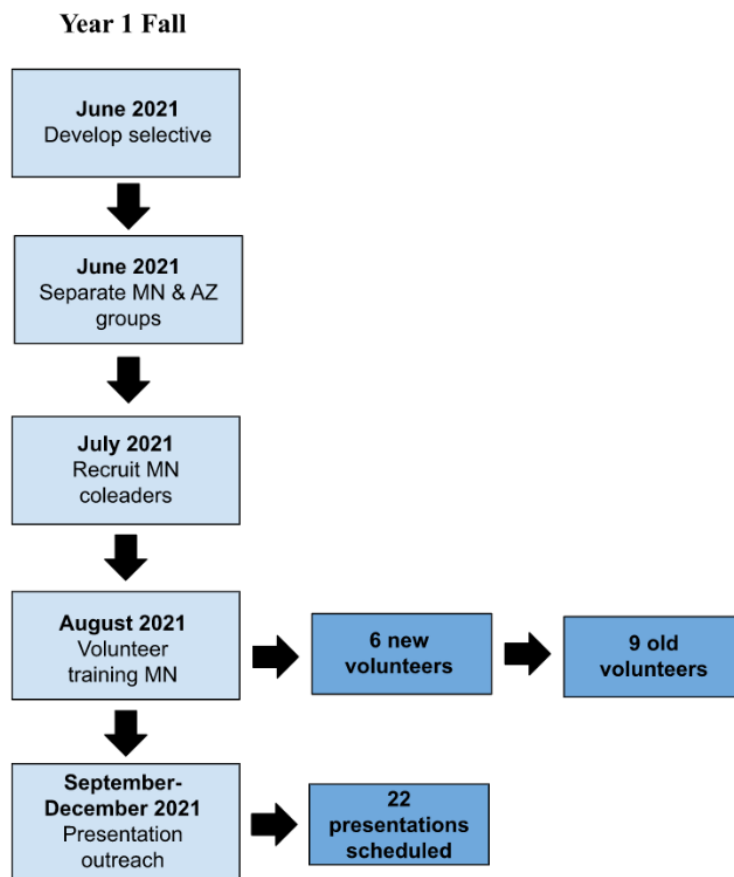


Figure 2. Framework, timeline, and results of the second half of year 1 (fall). AZ: Arizona, MN: Minnesota.



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Conflicts of Interest

None declared.

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Abbreviations

BTB: Block the Blaze

JWCF: John Wayne Cancer Foundation

MCASOM: Mayo Clinic Alix School of Medicine

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Short Paper

Evaluating the Public's Interest in Testicle Tanning: Observational Study

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Abstract

Background: A new and potentially dangerous health trend, *testicle tanning*, received extensive media attention following a popular television program where a health and fitness influencer touted that testicular tanning increases testosterone levels. It has been shown that the public has a particular interest in tanning *wellness* trends; thus, given the vague nomenclature of the practice, the abundance of misleading information and support for using UV light by other health influencers may lead to an increase in men exposing themselves to UV radiation and developing associated complications.

Objective: The aim of this paper is to evaluate the public's interest in testicle tanning.

Methods: Relative search interest was collected from Google Trends, and daily tweet volume was collected using Twitter via Sprout Social. The search was filtered to observe internet activity between February 1, 2022, and August 18, 2022. Autoregressive integrated moving average models were applied to forecast the predicted values through April 30 to compare to the actual observed values immediately following the airing of the show.

Results: We found that the relative search interest for testicle tanning peaked (100) on April 19, 2022, following a discussion of the topic on a television program. Compared to the forecasted relative search interest of 1.36 (95% CI –3.29 to 6.01), had the topic not been discussed, it showed a 7252% increase in relative search interest. A similar spike was observed in the volume of tweets peaking on April 18 with 42,736. The expected number of tweets from the autoregressive integrated moving average model was 122 (95% CI –154 to 397), representing a 35,053% increase.

Conclusions: Our results show that the promotion of testicle tanning generated significant public interest in an evidence-lacking and potentially dangerous health trend. Dermatologists and other health care professionals should be aware of these new viral health trends to best counsel patients and combat health misinformation.

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KEYWORDS

general dermatology; google trends; testicle tanning; UV radiation; public trends; skin cancer; cancer; harmful; internet; health trends; tanning

Introduction

“Testicle tanning” received extensive media attention following an episode of *Tucker Carlson Tonight*, where a health and fitness influencer touted that testicular tanning increases testosterone

levels. While first described as exposing one's scrotum to red-light therapy to enhance testosterone levels, this vague nomenclature and lack of supporting detail could mislead many into believing that exposure to UV light via sunlight or tanning beds will provide similar benefits. It has been shown that the

public has a particular interest in tanning “wellness” trends [1]; thus, in this observational study, we evaluate the public’s interest in testicle tanning.

Methods

Relative search interest (RSI; 0-100) was collected from Google Trends using the term “testicular tanning,” and from Twitter via Sprout Social (SproutSocial.com) using terms “testicular OR testicle OR ball OR balls OR scrotum” and “tan OR tanning OR sunning” to capture daily tweet volume. The search was filtered to observe internet activity between February 1, 2022, and August 18, 2022. Autoregressive integrated moving average models were applied to forecast the predicted values through April 30 to compare to the actual observed values immediately

following the show’s airing [2]. Peak differences were calculated with 95% confidence intervals to estimate spikes in data.

Results

We found that RSI for testicle tanning peaked (100) on April 19, 2022, following a discussion of the topic on the television program (Figure 1). Compared to the forecasted RSI of 1.36 (CI –3.29 to 6.01), had the topic not been discussed, this was a statistically significant difference, representing a 7252% increase in RSI. Continued search interest in testicular tanning was observed through August of 2022. A similar spike was observed in the volume of tweets peaking on April 18 with 42,736 (Figure 2). The expected number of Tweets from the autoregressive integrated moving average model was 122 (CI –154 to 397), a difference of 42,614, representing a 35,053% increase.

Figure 1. Search interest in "testicle tanning" from February 1, 2022, through August 18, 2022. L: lower; U: upper.

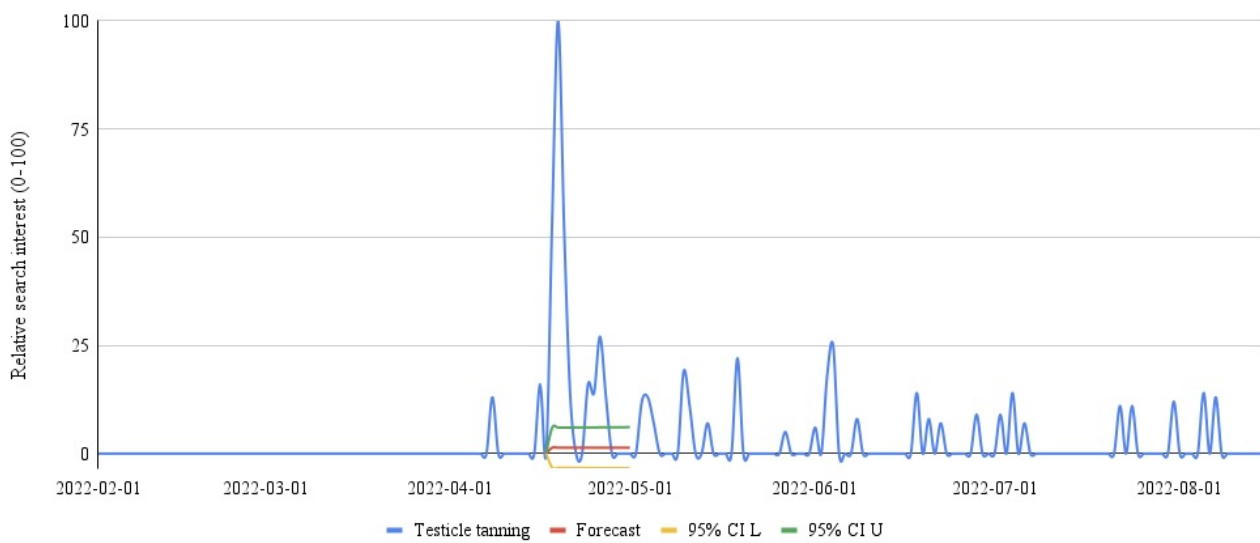
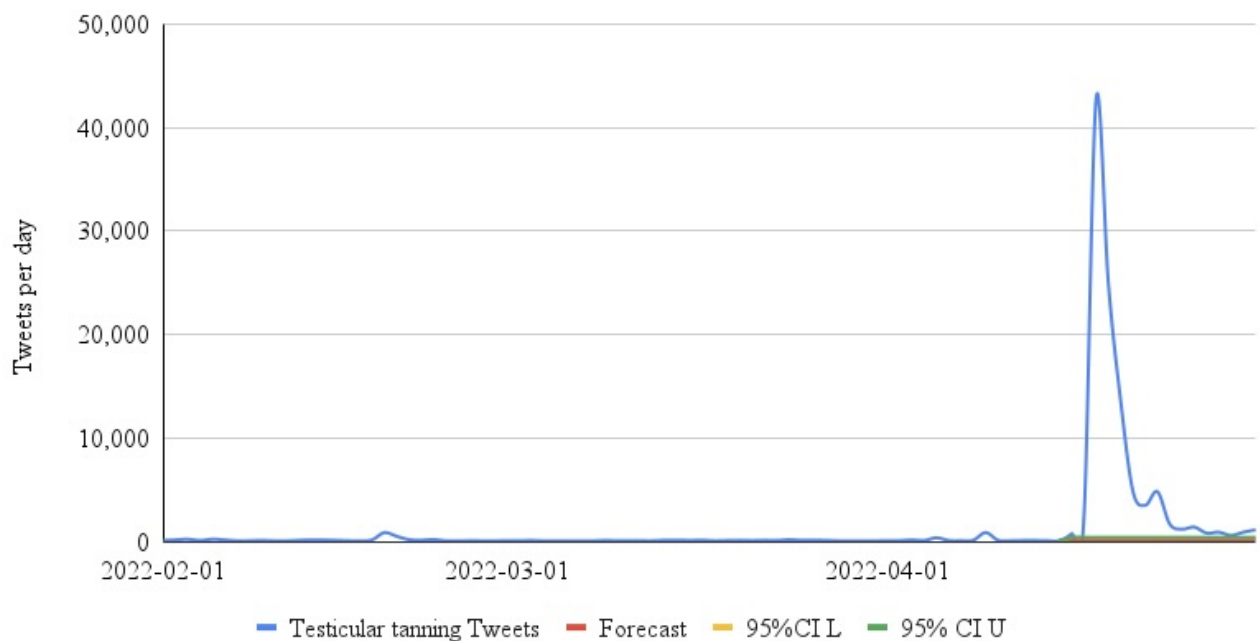


Figure 2. Daily number of tweets related to "testicle tanning" from February 1, 2022 to May 1, 2022. L: lower; U: upper.



Discussion

Similar to perineum sunning (a viral health trend performed by exposing one's anogenital area to direct sunlight) [1], our results show that the promotion of testicle tanning on this television program generated significant public interest in an evidence-lacking and potentially dangerous health trend. The interest in this topic may be partially explained by the immense attention and advertising men's sexual health and hormone replacement or hormone enhancing therapies receive in the US [3]. Although subsequent media coverage largely disfavored testicle tanning due to lacking evidence and potential dangers, other health influencers came to defend and encourage the practice of testicle tanning, specifically by using UV light [4]. Proponents of testicle tanning commonly cite a study from 1939, which found that in a small cohort of males all with "depressive mental states," UV irradiation to the genitals increased urinary androsterone (a metabolite of testosterone) levels by "nearly 200%" [5]. Beyond this questionable study, research has shown that exposure to UV radiation may increase sex steroid hormone levels; however, these studies either do not include human participants or do not specifically evaluate UV radiation

exposure to the genitals [6-8]. Research shows that excessive exposure to UV radiation may lead to higher rates of genital tumor formation and decreased sperm counts, as spermatogenesis is temperature dependent [9,10]. Thus, given the current obsession with optimizing male hormone levels, the high cost of red-light therapy, and misleading information and labeling of testicle tanning by prominent influencers, there may be an increase in men exposing themselves to UV radiation and developing associated complications. Limitations of our study include the retrospective cross-sectional design and the inability to determine the public's intent, which necessitates future research.

Our study highlights how a non-scientifically based and potentially dangerous tanning practice can generate significant public interest. Similar to our findings, in a previous study published by JMIR Dermatology, it was found that public interest in perineum sunning continued after the initial social media post went viral (and continues to trend in social and news media stories nearly 3 years later); therefore, dermatologists and other health care professionals should be aware of these new viral health trends to best counsel patients and combat health misinformation.

Conflicts of Interest

None declared.

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Abbreviations

RSI: relative search interest

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Original Paper

Experiences of Patient-Led Surveillance, Including Patient-Performed Teledermoscopy, in the MEL-SELF Pilot Randomized Controlled Trial: Qualitative Interview Study

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Abstract

Background: Current clinician-led melanoma surveillance models require frequent routinely scheduled clinic visits, with associated travel, cost, and time burden for patients. Patient-led surveillance is a new model of follow-up care that could reduce health care use such as clinic visits and medical procedures and their associated costs, increase access to care, and promote early diagnosis of a subsequent new melanoma after treatment of a primary melanoma. Understanding patient experiences may allow improvements in implementation.

Objective: This study aims to explore patients' experiences and perceptions of patient-led surveillance during the 6 months of participation in the MEL-SELF pilot randomized controlled trial. Patient-led surveillance comprised regular skin self-examination, use of a mobile dermatoscope to image lesions of concern, and a smartphone app to track and send images to a teledermatologist for review, in addition to usual care.

Methods: Semistructured interviews were conducted with patients previously treated for melanoma localized to the skin in New South Wales, Australia, who were randomized to the patient-led surveillance (intervention group) in the trial. Thematic analysis was used to analyze the data with reference to the technology acceptance model.

Results: We interviewed 20 patients (n=8, 40% women and n=12, 60% men; median age 62 years). Patients who were more adherent experienced benefits such as increased awareness of their skin and improved skin self-examination practice, early detection of melanomas, and opportunities to be proactive in managing their clinical follow-up. Most participants experienced difficulty in obtaining clear images and technical problems with the app. These barriers were overcome or persevered by participants with previous experience with digital technology and with effective help from a skin check partner (such as a spouse, sibling, or friend). Having too many or too few moles decreased perceived usefulness.

Conclusions: Patients with melanoma are receptive to and experience benefits from patient-led surveillance using teledermoscopy. Increased provision of training and technical support to patients and their skin check partners may help to realize the full potential benefits of this new model of melanoma surveillance.

KEYWORDS

melanoma; self-surveillance; digital technologies; teledermoscopy; teledermatology; mHealth; mobile phone

Introduction

Background

Globally, there is a large and growing number of people treated for melanoma localized to the skin who require ongoing surveillance for subsequent new melanoma [1]. Patients are recommended to attend routinely scheduled clinics at intervals varying between 3 and 12 months (clinician-led surveillance) to facilitate early detection of subsequent new primary or recurrent melanoma [2]. However, the optimum frequency and duration of follow-up and the clinical effectiveness of clinician-led surveillance are uncertain [3,4]. Many subsequent melanomas are detected by patients themselves, partners, or family members between scheduled visits [5,6].

These observations have led to the proposal of a new model of follow-up care called patient-led surveillance. This model involves regular and thorough skin self-examination (SSE), teledermatology facilitated monitoring, access to fast-tracked unscheduled clinic visits should the patient identify a lesion confirmed as concerning by the teledermatologist, and potentially fewer routinely scheduled clinic visits [7]. Mobile teledermoscopy is a *mobile health store and forward technology* in which patients use a mobile dermatoscope that attaches to their smartphone camera during their SSE [8]. A smartphone app is then used to process, track, and send high-quality images to a teledermatologist for assessment [9]. The adoption of mobile health technology interventions and telehealth is dependent upon their acceptance by patients and their treating clinicians [10,11]. Patients at risk of subsequent melanoma have reported that mobile teledermoscopy is acceptable when asked about its hypothetical use [9,12,13] and, in one study, after trying it out themselves (used on a one-off basis) [14].

Objectives

The MEL-SELF pilot randomized controlled trial (RCT) [15] (ACTRN12616001716459) compared 6 months of patient-led surveillance in addition to usual care (intervention) with clinician-led surveillance (usual care; control). The intervention was found to increase SSE frequency and thoroughness, clinic visit frequency, skin lesion excision, and diagnoses of subsequent new primary melanoma ahead of routinely scheduled visits, with no detectable effect on adverse psychological outcomes. Adherence to the intervention was suboptimal, with only half of the patients submitting any images for teledermatology because of withdrawals and nonresponse. In this nested qualitative study among a subset of intervention arm participants, we aimed to explore patients' perceptions and experiences of patient-led surveillance using mobile teledermoscopy, to understand possible determinants of adherence, and to identify opportunities for improving implementation of the intervention during the larger RCT.

Methods

Intervention Overview

The MEL-SELF pilot RCT was conducted from November 2018 to January 2020 and recruited 100 patients attending routine melanoma follow-up at 4 skin cancer clinics in Sydney and Newcastle, New South Wales, Australia (3 specialist-led clinics and 1 general practitioner-led clinic). Intervention arm participants were supported to undertake regular SSE and patient-performed teledermoscopy every 2 months. Teledermoscopy tools were provided by MetaOptima Technology Inc. [16], including a mobile dermatoscope (MoleScope I) that integrates with MoleScope (smartphone-based skin imaging app) [17] and DermEngine (a digital software system that facilitates the capture, storage, communication, and analysis of skin images by dermatologists) [18]. Each intervention arm participant also received a booklet of instructions and instructional videos. At the end of the 6-month study period, all 49 intervention arm participants were invited to participate in the qualitative study via postal mail and email, with follow-up invitations as needed.

Ethics Approval

This study was approved by the University of Sydney Human Research Ethics Committee (X15-0445) and the Royal Prince Alfred Hospital (HREC/15/RPAH/593). All participants provided informed consent. The reporting of this study followed the Standards for Reporting Qualitative Research [19].

Data Collection and Analysis

Semistructured telephonic interviews were conducted between February and March 2020. An interview guide ([Multimedia Appendix 1](#)) was developed by the authors, including the 2 consumer investigators (CL and DL). The interviews were conducted by 3 members of the research team, all trained in qualitative interviewing (EH, AM, and ES). The interviews were audio recorded and transcribed verbatim using a transcription service. Quantitative data on demographic and clinical characteristics and on adherence were collected as part of the pilot RCT using web-based surveys (REDCap [Research Electronic Data Capture; Vanderbilt University]) and the data analytics on image submission from the trial's teledermatology platform (DermEngine). RCT data regarding occupation were clarified and expanded upon in the qualitative interviews and then used to categorize the participants into occupation groups. Adherence data from the pilot RCT were used to group participants into categories of adherence, and then, we compared patient accounts between and within these categories. Preliminary codes were developed inductively from a subset of 6 transcripts [20] independently by 2 researchers, both experienced in thematic analysis (EH and DD). Preliminary codes and analytic memos were reviewed by the research team, which included researchers from a range of backgrounds, including clinical epidemiology, health psychology, behavioral

science, and health economics. The emerging themes were identified as analogous to the constructs of the technology acceptance model (TAM). The general TAM framework posits that a person's *intent to use* and *actual use* are predicated on their perception of the technology's *ease of use* (usability) and *usefulness* (benefit) [21] and has been used previously to assess the acceptability of apps to support health care delivery [22-29]. Thereafter, we used an inductive and deductive coding approach based on TAM [30]. Agreement between coders (DD and EH) was high, and discrepancies were resolved through consensus. The framework analytic method was used to organize codes, identify themes, and explain how they relate to each other [31]. Data saturation and interpretation were determined through ongoing coding of the remaining transcripts and discussions with the research team. Coding was performed in Microsoft Word, and Microsoft Excel was used for the thematic analysis using a data matrix.

Results

Overview

Of the 49 intervention arm participants invited, 43 (88%) responded and 20 (41%) agreed to participate in a telephone

interview. Interviews ranged in duration from 13 to 36 minutes. Those who participated in an interview were more likely to have submitted at least one image (16/20, 80%) compared with 53% (26/49) of intervention arm participants. Participants' demographics and frequency of image submission are summarized in Table 1. All interviewees thought that the intervention was a *useful concept* and a *great idea* for people treated for melanoma. They said that it could potentially provide quick access to an expert's opinion between scheduled visits and save time on physician's appointments, particularly for those who live at a distance from specialist services and would otherwise delay accessing care. We interpreted these hypothetical benefits (motivation to use the intervention) and reasons participants gave for not using the intervention at all as *intention to use*. Patterns of use throughout the trial follow-up (including no use) were interpreted as *actual use*. Figure 1 shows the adapted and extended TAM. Multimedia Appendix 2 includes additional illustrative quotes.

Table 1. Characteristics of qualitative study and total intervention arm participants.

Characteristics	Qualitative study participants (N=20)	Total intervention arm participants (N=49) ^a
Sex^b, n (%)		
Male	12 (60)	26 (54)
Female	8 (40)	22 (46)
Age (years), mean (SD; range)	57.4 (13.2; 28-78)	57.5 (12.3; 28-78)
Remoteness area (by postcode) [32]^c, n (%)		
Major cities (metro)	17 (89)	38 (88)
Inner regional (regional)	2 (11)	5 (12)
AJCC^d melanoma substage of first primary melanoma, n (%)		
0	7 (35)	18 (38)
IA	12 (60)	27 (56)
IB	1 (5)	3 (6)
Digital technology–related occupation (yes) ^{e,f} , n (%)	5 (25)	5 (10)
Time since first diagnosis (years), median (range)	4.7 (0.1-20.7)	5.5 (0.1-41.2)
Frequency of image submission (time points)^g, n (%)		
0	4 (20)	23 (47)
1	6 (30)	12 (25)
2	9 (45)	12 (25)
3	1 (5)	2 (4)
Total number of images submitted, median (range)	6.5 (0-32)	2 (0-35)
Melanomas detected at nonscheduled visits, n (%)	2 (10)	5 (10)

^aPercentages may not add to 100% because of rounding.

^bMissing data for 1 intervention arm participant.

^cMissing data for 1 qualitative study participant and 6 intervention arm participants.

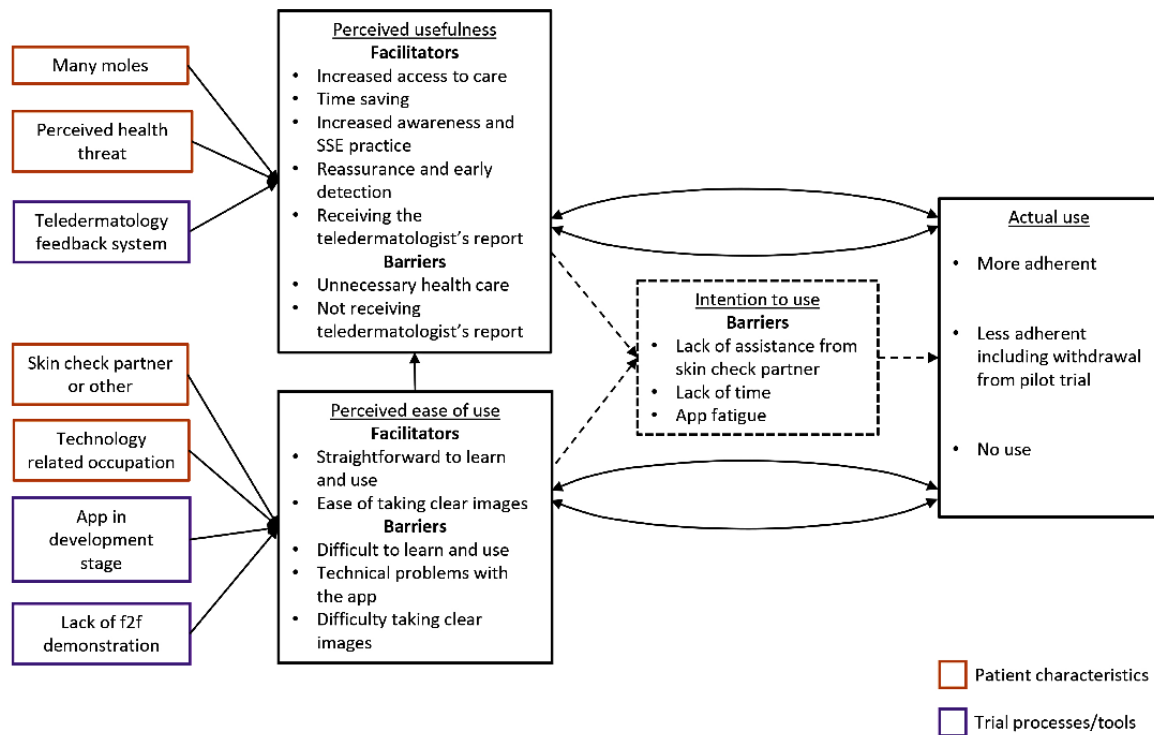
^dAJCC: American Joint Committee on Cancer, 8th Edition.

^eAn occupation was considered digital technology–related when primary work tasks involved working with apps, using advanced or programing software, or in information technology. *Retired* was counted as *no*.

^fData missing for 1 qualitative study participant and 7 intervention arm participants.

^gFrequency refers to image submissions where there was at least a 1-month interval between submissions. A total of 3 submissions indicated that images were submitted at all 3 time points (2, 4, and 6 months).

Figure 1. Adjusted and extended technology acceptance model for MEL-SELF pilot trial. f2f: face-to-face; SSE: skin self-examination.



Actual Use

Of the 20 intervention arm participants interviewed, 16 (80%) used the intervention tools to image lesions and submit them to a teledermatologist for review. Of these 16 participants, 1 (6%) submitted images at all 3 time points and 9 (56%) submitted images at 2 time points. These 10 participants (10/20, 50% of interviewees) were categorized as *more adherent*. Of the 20 participants, 6 (30%) submitted images at 1 time point; they are referred to as *less adherent*. The remaining (4/20, 20%) participants did not submit any images and were referred to as *nonadherent*. These 4 participants provided important data to help understand the high rate of nonadherence in the trial. One participant did not have a compatible smartphone, and 2 participants did not use the tools because of competing time commitments and the unavailability of their skin check partner. The fourth participant reported a sense of *tech overload* or *app fatigue* and did not want to use yet another app. All 4 participants believed that their existing routinely scheduled clinic follow-up visits were sufficient for melanoma surveillance.

Perceived Ease of Use

Skin Check Partner or Other Helper

Having a skin check partner was an eligibility criterion for participation in the pilot trial. Among the qualitative study sample, skin check partners included spouses, friends, or siblings. They were especially helpful for imaging difficult-to-view areas such as the back or back of the legs or when the lesion was on the participant's dominant hand or arm. All participants who reported helpful assistance from a skin check partner were among the more adherent, and some participants reflected that it would not be possible to use the intervention successfully without help. Apprehension about

using the technologies, mentioned by the 2 oldest patients aged 78 years and 73 years, was mitigated in both cases by having a *tech savvy* family member or skin check partner to assist:

I mean the technology is quite a bit new to us because we're in the older generation. But my grandson helped me get it going...so that worked out okay. [male, 78 years, regional, nondigital technology occupation]

However, having a nominated skin check partner did not always mean that they were available or were able to provide effective assistance. One participant reported that their skin check partner was reluctant to be involved and did not provide any help. Despite this, she persevered and submitted images at 2 time points, but she found the process difficult. Among those less adherent, only 1 participant mentioned having a helpful partner, and there was generally little mention of working together with someone to take images.

Digital Technology-Related Occupation

Participants who had the least amount of trouble learning to use the intervention tools and found the written instructions adequate tended to work in digital technology-related occupations. These participants were among the more adherent. When these participants encountered developmental glitches and *bugs* in the app (such as when indicating a newly identified mole on the full-body view or uploading and submitting images), they were able to recognize that these problems were most likely because of the app, rather than lack of their skill or knowledge. One participant said of the intervention that *the pros outweigh the cons* and subsequently persevered through problems with the app. Among participants who were less adherent, none worked in digital technology-related occupations and tended

to experience more frustration and uncertainty when they could not use or navigate the app with ease.

Taking Clear Images

Participants and their skin check partners were conscious of the importance of taking images of adequate quality. Participants who were more adherent tended to report that the dermatoscope was easy to use or did not mention any problems using the dermatoscope, whereas those who adhered less tended to be less confident. For them and their skin check partner, taking a good quality image became stressful and time consuming, involving *fiddling around* and taking several images before uploading one that they thought was of adequate quality. Some were unsure of the correct technique in terms of knowing the right amount of fluid or how much pressure to apply when holding the device against the skin.

Lack of Face-to-face Demonstration

The remaining 3 participants said that the instructions provided were adequate. Each of these 3 participants had a digital technology-related occupation. Of the 20 participants, 17 (85%) said that face-to-face training and demonstration would have been beneficial to make the process of learning to use a new technology more efficient and to increase their confidence in whether they were doing the *right thing*:

It would have made things easier. For instance, if there was a session where everyone was handed their little lens for the phone and to just have a practice and be told which part of the app to go to in which sequence for instance. [female, 60 years, metro, nondigital technology occupation]

Participants also said that face-to-face instruction would have provided an opportunity to ask for clarification of trial instructions such as how many moles to image per time point and an explanation of where the images were sent. Importantly, participants mentioned that because skin check partners were taking the images, they should be included in any demonstration and training:

My wife wasn't sure exactly...and I couldn't help her by not seeing where she was photographing...I couldn't know if she was doing it right or wrong, but I think it would've been easier for both of us to go up there and just get a demonstration, to make sure we did it right. [male, 63 years, Metro, nondigital technology occupation]

There was also a general sense of having to *get used to* the intervention, in terms of using the tools with confidence and integrating them into an SSE routine.

Perceived Usefulness

Increased Awareness and SSE Practice

Among those who had least difficulty in using the intervention and were more adherent, there was a strong sense of increased awareness of what was happening on their skin. This included looking more closely at moles that they would not have looked at otherwise and conducting more regular skin checks:

So, it gave me an opportunity—like it gives you a regime and it puts a tool in your hands, so it means that you pay more attention. [male, 53 years, metro, digital technology-related occupation]

Another participant felt empowered by being more involved in their melanoma follow-up:

So going on the trial was good because I could get that extra sense of control over what was happening with my moles. I could be watching it more carefully...it was an extra chance to be proactive. [female, 43 years, metro, digital technology-related occupation]

Another participant appreciated having easy access to a *track record* of concerning moles on their phone. For 2 participants, increased awareness of their skin caused additional anxiety because of the possibility of finding another melanoma; however, this did not detract from their perception of the usefulness of the intervention or impact their adherence.

Reassurance and Early Detection

Participants who were more adherent explained that they felt reassured with having access to additional care, meaning that concerning lesions were being monitored between scheduled appointments and, if necessary, action would be taken:

Well, you know that someone is checking on you monthly. So, to me, that's a good thing...And if they say to come back and get your doctor to check, well, really that's only for your benefit, isn't it? [female, 60 years, regional, nondigital technology occupation]

A total of 2 participants, also among those who were more adherent, highlighted their experience of the intervention's ability to facilitate the early detection of melanoma. They reported having a melanoma detected and diagnosed 2 months and 3 months ahead of their next routinely scheduled appointment:

Well, it picked up a melanoma, I thought that was just amazing, otherwise, it would have been another three months before they picked it up. [male, 73 years, metro, unknown occupation]

Having Many Moles

For the 4 participants who reported having dysplastic nevus syndrome, high perceived health threat influenced the stress and anxiety associated with the intervention. Three participants suggested that it may be more useful for people with fewer moles. Stress was caused by the possibility of not identifying moles of concern, not knowing which moles to image, having trouble finding the same mole that they had previously imaged, and having to arrange for additional clinic visits. These concerns were shared by the patients' skin check partners, who were tasked with ensuring that the images were of adequate quality. Of the 4 participants, 2 (50%) stopped using the intervention after submitting images at one time point, preferring to leave the responsibility of their skin examination solely to their physician:

It's stressful when somebody's asking, "What about this one? What about that one?" and at the end of

the day, if you're spending too much time it becomes, "Did we miss one?" or "Should we have put that one on?"...for me, I'd rather have him checking it every three months because of what I've been through for the past four or five years, you know. [male, 69 years, metro, nondigital technology occupation]

Of these 2 participants, 1 (50%) also found the tools very difficult to use, which compounded his frustration causing him to "chuck it [the intervention] in the too hard basket." The other 2 participants were among those who were more adherent. One participant reported that they would definitely keep using digital technologies beyond the trial if given the opportunity, and the other participant said that they would be unlikely to do so.

A total of 2 other participants said that confidence in using the intervention may increase if the moles to image were chosen with the physician, thereby reducing reliance on the participant's or skin check partner's ability to discern which moles were of most concern:

...maybe selecting the spots on your body in consultation with your doctor would make you feel more confident. [female, 60 years, metro, nondigital technology occupation]

Unnecessary Health Care Use

A total of 3 participants reported that the intervention resulted in unnecessary care. For 1 patient with many moles, the intervention prompted several additional clinic visits for lesions that were already being monitored by the treating physician. This caused the patient to question the usefulness of the additional visits, that had resulted in quite a lot of anxiety and an increase in health care costs. The need to image a prescribed minimum number of concerning moles also caused anxiety for this patient, as each additional mole photographed was potentially another skin cancer:

I've already had anxiety, but every time I submitted my pictures, I was told I had to find three or four—there was a requirement for moles that I needed to note if I detected changes or wanted to be monitored and obviously, you're like, "I guess I've got to find another one." [female, 43 years, metro, digital technology-related occupation]

Another participant, also with many moles, recounted that having to look for a prescribed number of new concerning moles was not helpful, as he did not know which ones to choose from. In addition, in the fast-tracked appointment that he was requested to make, it turned out that an image of a stretched lesion in which too much pressure had been applied had prompted the recommendation. A third participant, who had very few moles, felt that the intervention was not useful for them because they felt compelled to submit images of lesions they were not concerned about. This participant was among those who were less adherent. It is important to highlight these instances of unnecessary care; however, they did not have a clear effect on adherence.

Receiving the Teledermatologist's Report

Feedback from a teledermatologist was received successfully by some participants, one saying that the response time was excellent. However, for others, the lack of timely feedback from the teledermatologist put the usefulness of the intervention into question. Technical problems with the teledermatology feedback loop including absence of a *sent* confirmation or not receiving the teledermatologist's report at all resulted in uncertainty. Participants explained that they were not sure if they had used the intervention correctly, if the images had been received at the other end, or if they were required to make an appointment with their physician:

...this happened a couple of times, when I submitted something that I felt was unusual...nothing came back, I didn't get a response, I didn't get a report from the specialist on the receiving end...So, I think there was a little bit of a disconnect initially... [male, 53 years, metro, digital technology-related occupation]

Receiving the teledermatologist's report also caused anxiety for some participants, but not more anxiety than they experienced when receiving other test results about their melanoma risk. The use of the word *urgent* in the teledermatologist report provoked some alarm, but this was balanced by the reassurance of knowing that if another melanoma was suspected, then action could be taken. Receiving the teledermatologist's report is integral to the usefulness of the intervention; however, whether receiving feedback had a clear impact on adherence is difficult to discern, as most accounts of problems with feedback came from those who were more adherent and for whom there were more opportunities for problems to occur.

Discussion

Principal Findings

In this qualitative study of patients randomized to patient-led melanoma surveillance using teledermoscopy, we found that, in practice, among participants who were more adherent (submitted images at 2 or 3 time points), the intervention prompted increased awareness of their skin and SSE practice, reassurance, and early detection of subsequent melanoma. These more adherent participants were those who found the intervention easier to use because of working in a digital technology-related occupation and by having an effective skin check partner. Those who submitted images at only 1 time point found the tools too difficult to use. This outweighed the perceived potential benefits and impacted their intention to use the intervention tools. Although a few participants found the intervention tools easy to use from the start, most participants experienced varying degrees of difficulty in taking clear images and encountered several developmental glitches and navigational issues in the app. These participants needed repeated practice before they found the tools easier to use. Perceived usefulness was lower in people with many moles, especially when it prompted unnecessary clinic visits. Those who did not submit any images explained that their nonadherence was because of competing time commitments, not having an available skin

check partner, not having a compatible mobile phone, or *app fatigue*.

In our study, anxiety was not a clear delineating factor between those who were more or less adherent; however, it was present in the experiences of most participants and their skin check partners. High perceived health threat associated with a personal history of melanoma, increased patient and skin check partner anxiety, particularly among those with many moles. Accounts of stress and anxiety among these patients in our study and in other studies suggest that patients with many moles may require more ongoing support to conduct patient-led melanoma surveillance because of difficulty in selecting moles and increased risk [14,33].

Aligning with the core hypotheses of the TAM framework [21], we found that ease of use and usefulness influenced intent to use and actual use. However, we also found that despite the initial intention to use, perceptions of ease of use and usefulness after the follow-up period were more influential in explaining actual use. Our findings also indicate that actual use impacted ease of use and usefulness, in that those who used the intervention over a longer period found it easier to use (after getting used to it) and experienced more of its benefits. TAM is commonly used to assess factors that influence the intention to use health technologies. Intention to use is interpreted as a measure of acceptability [23,25,27], even when participants are only asked about hypothetical use [26] or it is not clear if all participants have used the technology [29]. In studies that include actual use in their final TAM model, intention to use is not always a strong or statistically significant predictor of actual use [24,25]. Intention to use, measured hypothetically or after a short period of use, may not always be a good predictor of actual use behavior [28], particularly when digital technology requires a period of learning and is being used in the management of high-risk conditions. Qualitative assessment *after* implementation, and over time, may produce a more accurate and comprehensive understanding of context and patient and intervention characteristics that influence actual use behavior [34] to better inform implementation strategies.

Overwhelmingly, participants suggested that training and demonstration were necessary for themselves and their skin check partner. One-to-one training in SSE has been found to result in greater SSE skill acquisition compared with a paper workbook or electronic interactive training [35]. Previous research has found that a partner's attendance at SSE skills training increased the frequency of SSE [36,37]. A patient and partner working together as a *dyad* has also been found to improve SSE practice [38]. In their assessment of mobile teledermoscopy, Horsham et al [14] found that most participants had the help of a family member to take photos and submit images. However, the necessity of having a skin check partner excludes people who do not have someone to help them take images regularly, and further consideration is needed on how to best support these people to undertake regular self-surveillance and act on their results.

The lack of image submission by almost half of all intervention participants in the pilot RCT could be explained by the additional effort and time needed to learn to use the intervention

and then use it routinely with a skin check partner, in addition to usual care. When combined with a high perceived health threat from their increased melanoma risk, this may mean that some patients prefer to rely solely on their physician for follow-up care [7,34]. However, early one-on-one training and demonstration may make the learning process less daunting, encourage participation of skin check partners, and create a supportive connection between trial staff and participants. This may encourage more participants to try the intervention and to continue to engage with it over a longer term. Among our study sample, those who used the intervention over a longer period reported more positively on ease of use and usefulness, highlighting the importance of supporting skill acquisition to increase self-efficacy.

Our findings have assisted in refining the design and implementation of a larger ongoing RCT on patient-led melanoma surveillance [39], and several changes have been made. To help overcome barriers to perceived usefulness, particularly for those with many moles, a *target lesion* will be selected by the treating clinician, an approach suggested in previous studies [9,40]. To reduce the potential for medical overuse [41], the need for a minimum number of lesions has been removed. If the patient does not have other lesions of concern, they will not need to submit any images other than those of the target lesion. Clinical practice guidelines consistently recommend that patients should be taught SSE, but the optimum frequency of SSE and teledermatology remains ill-defined [42]. The frequency of image submission requested in the pilot trial was assessed to be too high, as only a small proportion of participants in the pilot RCT, including only 1 qualitative study participant, were able to submit images at all 3 time points [15]. The frequency of image submission will be reduced from every 2 months to every 3 months. All intervention arm participants and their skin check partners will be encouraged to participate in one-to-one demonstration sessions with the study staff, in addition to receiving instructional videos and written instructions. The study staff will also be available for the duration of the follow-up period to assist patients with troubleshooting. In addition, the technology provider has made several improvements to the app and teledermatology feedback system, which addresses the technical difficulties experienced by the participants, including nonreceipt of the teledermatologist's report.

The patient-led surveillance approach has the potential to partially (or completely) replace routinely scheduled visits. However, during this initial stage in which we are evaluating the safety and effectiveness of the intervention, we have implemented it in addition to usual care, both in the pilot trial that this study relates to and the larger trial that is ongoing. In the process of co-designing these studies, it was clear that both clinicians [43] and patients [12] preferred implementation in addition to usual care as a first step before considering circumstances in which it might replace (in part or in whole) routinely scheduled visits. Although we implemented the intervention in addition to usual care, we are surveying patients regarding their acceptance of a hypothetical reduction to their routinely scheduled clinic visits. We envision that this may inform situations in which the intervention might replace some

routinely scheduled visits. Data from interviews with clinicians involved in the pilot trial were also informative. The clinicians indicated that after experiencing the actual use of the intervention in the pilot trial, they anticipated that in some clinical scenarios, it may replace routinely scheduled visits—in particular, where a specific lesion is being monitored for change (these findings have recently been corroborated; Drabarek, D, unpublished data, May 2022). In other scenarios, it may be used in addition to usual care to triage which patient concerns warrant review in the clinic—in particular, where a new lesion needs evaluation. Further exploration of these different uses of patient-led surveillance, the patients most likely to benefit from this approach, and integration with other approaches to surveillance [44] could help to define how it may be used in the most clinically effective and cost-effective way.

Strengths and Limitations

As our findings draw on patient experiences over the 6-month trial period, they provide novel insights into the implementation of patient-performed teledermoscopy interventions. As the study period allowed for repeated use of the intervention tools, we were able to interrogate a variety of adherence patterns and identify facilitators and barriers to these and their determinants. These findings have assisted in anticipating and mitigating the risk factors for low adherence in the larger MEL-SELF trial and may also be useful for future studies. Our findings also draw on the experiences of a study sample with variations in relevant demographic characteristics such as age, residing in metropolitan or regional areas, and digital technology self-efficacy. However, as an opt-in recruitment method was used, the qualitative

substudy sample was much more adherent than those who did not agree to participate in an interview; thus, additional explanations for nonadherence may have been missed. Further research is necessary to understand the low uptake of mobile teledermoscopy interventions among patients. In addition, some aspects of the results reflect the use of software that was in its development phase, and the findings may not be transferrable to patients using teledermoscopy technologies created by different developers. A time frame longer than 6 months may have revealed further determinants of actual use. Finally, because interviews were conducted at the end of the pilot trial, experiences of learning to use the intervention tools at the beginning of the trial may not always have been reported accurately.

Conclusions

Patient-led surveillance is a complex behavioral change intervention. It aims to improve patients' knowledge, skills, and confidence in performing SSE using digital technologies so that they are better able to detect and act on concerning changes to moles and other skin lesions. Understanding how and why patients do or do not use this intervention is fundamental to increasing adherence within a clinical trial setting and increasing uptake in clinical practice, if it is found to be a clinically beneficial and cost-effective method of melanoma surveillance. Ultimately, it may allow access to melanoma follow-up care regardless of geographical location [45] and could become a *new normal* method of surveillance after the COVID-19 pandemic [46].

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Authors' Contributions

KLJB, JH, MJ, CL, and DL contributed to the conception and design of the study. AM and ES contributed to the acquisition of data. DD, EH, MJ, JH, KLJB, and DA contributed to the analysis and interpretation of data. DD and EH drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content and gave approval for its publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Interview topic guide.

[[DOCX File, 50 KB - derma_v5i3e35916_app1.docx](#)]

Multimedia Appendix 2

Illustrative quotations.

[[DOCX File, 23 KB - derma_v5i3e35916_app2.docx](#)]

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Abbreviations

NHMRC: National Health and Medical Research Council

RCT: randomized controlled trial

REDCap: Research Electronic Data Capture

SSE: skin self-examination

TAM: technology acceptance model

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Review

Store-and-Forward Images in Tele dermatology: Narrative Literature Review

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Abstract

Background: Store-and-forward (SAF) tele dermatology uses electronically stored information, including patient photographs and demographic information, for clinical decision-making asynchronous to the patient encounter. The integration of SAF tele dermatology into clinical practice has been increasing in recent years, especially during the COVID-19 pandemic. Despite this growth, data regarding the outcomes of SAF tele dermatology are limited. A key distinction among current literature involves comparing the quality and utility of images obtained by patients and trained clinicians, as these metrics may vary by the clinical expertise of the photographer.

Objective: This narrative literature review aimed to characterize the outcomes of SAF tele dermatology through the lens of patient- versus clinician-initiated photography and highlight important future directions for and challenges of the field.

Methods: A literature search of peer-reviewed research was performed between February and April 2021. Key search terms included *patient-initiated*, *patient-submitted*, *clinician-initiated*, *clinician-submitted*, *store-and-forward*, *asynchronous*, *remote*, *image*, *photograph*, and *tele dermatology*. Only studies published after 2001 in English were included. In total, 47 studies were identified from the PubMed electronic database and Google Scholar after omitting duplicate articles.

Results: Image quality and diagnostic concordance are generally lower and more variable with patient-submitted images, which may impact their decision-making utility. SAF tele dermatology can improve the efficiency of and access to care when photographs are taken by either clinicians or patients. The clinical outcomes of clinician-submitted images are comparable to those of in-person visits in the few studies that have investigated these outcomes. Coinciding with the onset of the COVID-19 pandemic, asynchronous tele dermatology helped minimize unnecessary in-person visits in the outpatient setting, as many uncomplicated conditions could be adequately managed remotely via images captured by patients and referring clinicians. For the inpatient setting, SAF tele dermatology minimized unnecessary contact during dermatology consultations, although current studies are limited by the heterogeneity of their outcomes.

Conclusions: In general, photographs taken by trained clinicians are higher quality and have better and more relevant diagnostic and clinical outcomes. SAF tele dermatology helped clinicians avoid unnecessary physical contact with patients in the outpatient and inpatient settings during the COVID-19 pandemic. Asynchronous tele dermatology will likely play a greater role in the future as SAF images become integrated into synchronous tele dermatology workflows. However, the obstacles summarized in this review should be addressed before its widespread implementation into clinical practice.

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KEYWORDS

store-and-forward; patient; clinician; telehealth; COVID-19; tele dermatology; image; photograph; asynchronous; practice; outcome

Introduction

The role of telecommunications in clinical dermatology (teledermatology) is continually expanding as technology becomes an inextricable component of medical practice. The COVID-19 pandemic has driven it to the forefront of many dermatology practices around the world, often with rapid implementation spurred more by necessity than methodology. Teledermatology can be classified by the temporal relationship between the clinician's decision-making and the patient encounter. Synchronous teledermatology takes the form of web-based, real-time patient visits and is outside the scope of this review. Asynchronous, or store-and-forward (SAF), teledermatology uses electronically stored information, such as patient photographs and demographic information, for medical decision-making.

Data on SAF teledermatology vary considerably depending on how studies are structured. A key element of experimental setup is whether the SAF images are acquired by a trained clinician or the patient. Intuitively, variation in the quality and utility of patient-submitted images is to be expected. These characteristics may depend on whether a patient possesses a high-quality camera, their understanding of clinical photography, and their access to assistance with taking photographs—elements that are more readily available in the clinical setting. Characterizing the differences in SAF images submitted by clinicians versus patients is crucial as more health care systems integrate teledermatology consultation programs into clinical practice. Given the lack of comprehensive articles regarding this distinction, this review will explore the outcomes, consider the impacts of COVID-19, and highlight the future directions of asynchronous teledermatology based on whether photographs are taken by clinicians or patients.

Methods

A narrative review of peer-reviewed literature was performed between February and April 2021 to identify articles pertaining to SAF teledermatology with clinician- and patient-initiated images. Key search terms included *patient-initiated*, *patient-submitted*, *clinician-initiated*, *clinician-submitted*, *store-and-forward*, *asynchronous*, *remote*, *image*, *photograph*, and *teledermatology*. The study designs of the identified literature included a meta-analysis, systematic reviews, randomized controlled trials, and observational studies.

Only studies published after 2001 were included in the search criteria, although a substantial number of articles related to SAF teledermatology were published in the past decade. In total, 47 studies were selected from the PubMed electronic database and Google Scholar after omitting duplicate articles. Inclusion criteria consisted of articles that primarily examined the clinical aspects of SAF teledermatology, such as diagnosis, waiting intervals, change in management, clinical outcomes, and image quality. Survey studies and observational reports were also included if they primarily focused on the use of SAF teledermatology in patient care. Studies that investigated synchronous but not asynchronous teledermatology, focused on SAF teledermatology outside of patient care (eg, economic

analyses), and were not available in English were excluded. In total, 2 independent researchers with knowledge of study interpretation and literature review performed separate screenings of the literature and validated their search results. Several studies in this review met the exclusion criteria but were included as discussion points rather than for result interpretation.

Results

Image Quality

The evaluation of a photographed skin condition can be heavily influenced by its image quality. Several studies that assessed images taken by trained clinicians found that those deemed of low or poor quality ranged from approximately 5% to 20% [1-4]. In contrast, the quality of patient-initiated images is more variable. One study of patients who submitted smartphone images of their skin lesions to dermatologists found that around half took their own photographs [5]. The authors excluded nearly 10% of the images from assessment due to poor image quality [5]. Given that this study population consisted of university students, the number of poor-quality images could be much higher in populations with lower technological proficiency or those without assistance in capturing photographs [5]. Other studies with similar experimental setups have observed that low-quality images comprised approximately 10% to 40% of all patient-submitted photographs [6-8]. Though data indicate that clinician-initiated images are generally higher quality than patient-initiated images, standardizing the photography of skin conditions may be useful for teledermatologists receiving primary care referrals and direct patient messages. For instance, tools in the electronic health record (EHR) could remind patients and referring clinicians to provide images with the appropriate lighting, field of view, and focus [9].

Diagnostic Agreement and Accuracy

Interrater agreement refers to the degree to which the responses of 2 or more raters are similar [10]. When responses pertain to the diagnosis of a disease, it is called diagnostic agreement or concordance, which can be reported as exact agreement between evaluators or as the sum of exact agreement and weighted partial agreement of categorically similar diagnoses [11]. The diagnostic concordance rates between teledermatologists evaluating SAF images and dermatologists seeing patients face-to-face (FTF) range from approximately 60% to 90% for the studies included in this review [2-4,12,13] (Table 1). One study found that the agreement between 2 dermatologists who evaluated images remotely was 68% compared to 88% concordance when these same dermatologists evaluated patients at a FTF visit [3] (Table 1). A recent meta-analysis found that FTF diagnostic concordance rates are significantly higher than remote concordance rates, although the study did not stratify by whether the SAF images were generated by clinicians or patients [14]. Notably, 3 of the 6 studies included in the meta-analysis were published prior to 2000, indicating a need for more up-to-date research [14]. Another consideration that may impact diagnostic concordance is the training and practice setting of the referring clinician. Pasadyn et al [15] identified that diagnostic agreement was highest (50%) between teledermatologists and physicians referring from office visits,

compared to teledermatologists and nurse practitioners, physician assistants, or physicians referring from walk-in clinics (around 30%; [Table 1](#)).

Recent evidence suggests that the diagnostic utility of SAF images depends on lesion type. [Warshaw et al \[1\]](#) found that diagnostic concordance between SAF images evaluated by a

teledermatologist and those same conditions examined in-person were higher for pigmented lesions than nonpigmented lesions. Interestingly, they observed that concordance between management recommendations made by a teledermatologist and an in-person dermatologist was lower when evaluating pigmented lesions, which may be in part due to the option to write in answers for decision-making [\[1\]](#) ([Table 1](#)).

Table 1. Diagnostic outcomes for store-and-forward teledermatology. The results are reported as percentage exact agreement or percentage exact and partial agreement with a 95% CI.

Type	Setting	Sample	Outcome	Reference
Clinician-initiated				
Observational	Single-center study in the United States (Minnesota)	2152 patients	52.8% to 93.9% diagnostic agreement for pigmented lesions, 47.7% to 87.3% diagnostic agreement for nonpigmented lesions, 66.7% to 79.8% management agreement for pigmented lesions, and 72% to 86.1% management agreement for nonpigmented lesions	Warshaw et al [1]
Observational	Single-center study in the United States (Wisconsin)	135 children	82% agreement between TD ^a and FTF ^b diagnosis (95% CI 73%-88%)	Heffner et al [2]
Observational	Web-based app in Sweden	40 adults	68% interobserver agreement for TD diagnosis (95% CI 51%-81%), and 88% interobserver agreement for FTF diagnosis (95% CI 73%-96%)	Börve et al [3]
Systematic review	N/A ^c	25 studies	62% to 89% agreement between TD and FTF diagnosis	Rat et al [4]
Observational	Single-center study in Austria	18 adults	89% exact agreement between TD and FTF diagnosis	Massone et al [12]
Observational	Single-center study in the United States (California)	86 adults	82% agreement between TD and FTF diagnosis (95% CI 73%-89%)	Lamel et al [13]
Observational	Single-center study in the United States (Ohio)	318 clinic visits	MD ^d /DO ^e : 50% exact diagnostic agreement between TD and office visit, and 29.8% exact diagnostic agreement between TD and walk-in clinic; NP ^f /PA ^g : 33.8% exact diagnostic agreement between TD and office visit, and 34% exact diagnostic agreement between TD and walk-in clinic; diagnostic agreement was higher for MD/DO office visits than MD/DO walk-in clinics ($P=.021$), NP/PA office visits ($P=.035$), and NP/PA walk-in clinics ($P=.022$)	Pasady et al [15]
Patient-initiated				
Observational	Single-center study in Australia	55 adults	69% exact agreement between TD and FTF diagnosis	Boyce et al [5]
Observational	Single-center study in Austria	263 adults	49% exact agreement between TD and FTF diagnosis ^h ; significant correlation between correct diagnosis and image quality ($P<.001$)	Weingast et al [8]
Randomized controlled trial	Single-center study in the United States (Pennsylvania)	40 children	83% agreement between TD and FTF diagnosis (95% CI 71%-94%)	O'Conner et al [16]
Observational	Single-center study in the Netherlands	96 adults	41% exact agreement between TD and FTF diagnosis	Eminović et al [17]

^aTD: teledermatology.

^bFTF: face-to-face.

^cN/A: not applicable.

^dMD: Doctor of Medicine.

^eDO: Doctor of Osteopathic Medicine.

^fNP: nurse practitioner.

^gPA: physician assistant.

^hIncludes cases that dermatologists indicated as not possible to diagnose.

Compared to clinician-initiated images, patient-initiated images have diagnostic concordance rates that are lower and more

variable. Several studies indicate that diagnostic concordance rates between dermatologists evaluating patient-generated SAF

images and dermatologists evaluating patients at a FTF visit range from approximately 40% to 80% [5,8,16,17] (Table 1). One of these studies used patient-acquired dermoscopic images to monitor atypical nevi, indicating that patients may be able to acquire highly useful images when provided adequate instructions [18]. Importantly, Weingast et al [8] observed that diagnostic agreement significantly correlated with image quality. The current literature on patient-initiated images is limited by the generalizability of the patient cohorts due to the dearth of studies. For instance, 2 studies had mean ages of 36 and 39 years, whereas 2 other studies were conducted in the pediatric setting in which parents took photographs of their children [6,8,16,17] (Table 1). Such groups may have more technological proficiency than the average adult dermatology patient, which could skew these studies toward higher estimates of image quality than in actual practice.

Diagnoses based on SAF teledermatology images can also be compared to histopathological reports, referred to here as diagnostic accuracy. A recent study found that the diagnostic accuracy of clinician-initiated images was higher for malignant diagnoses such as melanomas and nonmelanoma skin cancers than benign diagnoses [19]. However, there was higher interobserver concordance between teledermatologists and in-person dermatologists when they examined benign diagnoses [19]. To date, there are no studies that evaluate the diagnostic accuracy of patient-initiated images.

In summary, the rates of diagnostic concordance between SAF teledermatology and FTF clinic visits are higher and less variable when skin conditions are photographed by clinicians. Agreement can be impacted by several factors, including the practice type of the referring clinician, type of lesion being photographed, and image quality. Studies that evaluate the diagnostic outcomes of patient-initiated SAF images in a real-life setting are needed.

Change in Condition, Waiting Interval, and Other Clinical Outcomes

Aside from diagnostic concordance, other outcomes that are relevant to SAF teledermatology may include change in a skin condition and waiting interval between consultation and appointment, among several others. For images taken by clinicians, outcomes appear to be generally similar between SAF teledermatology and FTF visits (Table 2). A prospective study by Pak et al [20] found that the clinical outcomes of asynchronous consults and conventional in-person visits were not significantly different based on a 3-point scale rated by a dermatologist, with 65% and 64% of clinical outcomes being rated as improved in the usual care group and the teledermatology group, respectively (Table 2). Whited et al [21] conducted a randomized controlled trial comparing outcomes

at 3-month and 9-month timepoints after primary care physician (PCP) referral [21]. They found no significant difference in the quality-of-life metric Skindex-16 at these timepoints between patients randomized to SAF or conventional consultations [21] (Table 2).

Several studies investigated the waiting intervals between initial consultation and subsequent clinic visit for clinician-initiated SAF teledermatology and traditional referral systems. They all found that SAF teledermatology significantly reduced the time between referral and clinic visit [22-24]. One study observed that SAF teledermatology referral not only reduced the time until consultation completion but also the time to biopsy and surgery for applicable patients [23]. The benefit of this reduced waiting interval may have contributed to the adoption of electronic dermatology referrals over traditional letter referrals in many health care systems.

The clinical outcomes of patient-submitted images are mostly descriptive in nature. Hubiche et al [6] found that SAF images taken prior to in-person evaluation changed treatment decisions in 36% of patients (Table 2). Notably, skin lesions had changed in 87% of patients at in-person evaluation compared to prior photographs [6]. This may indicate that patient images provide useful information for tracking the evolution of a skin condition. However, it is possible that the additional information may in fact obfuscate the correct diagnosis and management, given that the study did not examine any further outcomes [6] (Table 2). Regarding waiting interval, one study that implemented a direct-care teledermatology program reported an average time of <1 day from patient concern to teledermatologist assessment [25]. Eminović et al [17] used SAF teledermatology as a triage tool based on patient-submitted images collected by their PCPs. The authors found that 23% of patients could have avoided FTF appointments, as determined by a panel of 3 dermatologists [17] (Table 2). Notably, there is a lack of data comparing the outcomes of SAF teledermatology based on patient-submitted images to other forms of care, such as FTF care and clinician-initiated teledermatology. As more health care systems allow patients to directly send photographs to their dermatologists, elucidating these outcomes becomes increasingly important.

In summary, outcomes such as change in condition and the quality of life between clinician-initiated SAF teledermatology and FTF care are not significantly different. However, there are a limited number of studies that examine clinically relevant outcomes, and more research is needed. Waiting intervals between SAF referral and FTF appointment are significantly decreased compared to conventional referral systems. Patient-initiated images could supplement decision-making but lack comparable outcomes to other forms of dermatologic care.

Table 2. Clinical outcomes of store-and-forward teledermatology.

Type	Setting	Sample	Outcome	Reference
Clinician-initiated				
Observational	2-center study in the United States (Texas)	508 adults	No significant difference between TD ^a (65% improved, 32% unchanged, and 3% worsened) and FTF ^b care (64% improved, 33% unchanged, and 4% worsened) as rated by a 3-point clinical course scale ($P=.57$)	Pak et al [20]
Randomized controlled trial	2-center study in the United States (Missouri and Minnesota)	326 adults	No significant difference between TD and FTF care as evaluated by Skindex-16 at 3 ($P=.66$) and 9 ($P=.39$) months	Whited et al [21]
Observational	Multicenter study in Spain	2009 adults	51.2% of patients with TD consults not referred to FTF clinic; waiting interval to clinic appointment was 12.31 (95% CI 8.22-16.40) days for TD referral and 88.62 (95% CI 38.42-138.82) days for traditional letter referral system	Moreno-Ramirez et al [22]
Observational	Single-center study in the United States (California)	149 adults	Mean time interval for TD versus conventional referral was 4 versus 48 days ($P<.0001$) for initial consult completion; 38 versus 57 days ($P=.034$) for time to biopsy; and 104 versus 125 days ($P=.006$) for time to surgery	Hsiao et al [23]
Randomized controlled trial	Single-center study in France	103 patients	Waiting interval to clinic was 4 days for TD referral and 40 days for conventional letter referral system ($P<.01$)	Piette et al [24]
Patient-initiated				
Observational	Single-center study in France	162 adults and children	Photographs of a skin lesion taken before a clinic visit changed treatment decisions in 36% of patients	Hubiche et al [6]
Observational	Single-center study in the Netherlands	105 adults and children	23% of patients could have avoided FTF care, as determined by 3 dermatologists	Eminović et al [17]
Observational	Single-center study in the United States (California)	38 adults	Average time from patient concern to consultation was 0.8 (SD 1) days, and 75% of concerns could be managed remotely	Pathipati et al [25]

^aTD: teledermatology.

^bFTF: face-to-face.

Access to Care

One practical advantage of asynchronous teledermatology is the potential to expand health care access to underserved populations (Figure 1). Several urban programs have used images obtained during PCP visits for SAF teledermatology consultation in safety-net health care systems [26-29]. All of the studies found that asynchronous consultation resulted in substantially reduced waiting periods for dermatologic care compared to traditional referral systems [26-29]. One study in particular found that the no-show rate for referral via SAF consultation was around 60% of the no-show rate through

traditional referral [29]. SAF teledermatology consultation has also been studied in rural populations, though outcomes have largely been limited to clinician questionnaires and economic analyses [30,31]. As health care systems expand access to dermatologic care and reduce waiting intervals via asynchronous consultation, other clinically relevant outcomes such as improved quality of life and prevention of disease should be reported in future studies. Excitingly, the American Academy of Dermatology has recently introduced a telemedicine program that uses SAF media from referring clinicians to provide care to underserved US populations [32].

Figure 1. Barriers and advances to the integration of store-and-forward teledermatology into clinical practice.

Barriers:

- Low quality images
- Lack of a definitive reimbursement model
- Heterogeneity and low generalizability of outcomes
- Privacy and ethics regulations
- Lack of widespread integration into electronic health records



Advances:

- Health care access for disadvantaged populations
- Algorithms for inpatient dermatology consultation
- Utility during COVID-19 pandemic
- Hybrid synchronous and asynchronous models

Impact of COVID-19

Outpatient Management

The COVID-19 pandemic necessitated many clinics to temporarily adopt teledermatology for all patient encounters. Although most teledermatology visits were synchronous, asynchronous visits drastically increased from prior years [33-35]. For example, one program reported 3 asynchronous visits in April 2019 and 197 asynchronous visits in April 2020, increasing from <1% of all patient encounters to approximately 10% [33,34]. Another group reported that the average number of daily teledermatology consultations received increased from 9.28 to 36.4 following an alert regarding the potential cutaneous manifestations of COVID-19 [36].

Several important considerations arose following the widespread adoption of teledermatology. For patients who communicated directly with their dermatologists, it was important to explore whether the circumstances that used their self-acquired SAF images were appropriate. Das et al [37] used patient-submitted images to adjust isotretinoin dosing in established acne patients and discovered no significant difference in the dosing regimens between synchronous and asynchronous visits. A group in Spain used a direct-to-patient teledermatology mobile app to evaluate new patients who submitted their own photographs [38]. Since the most common conditions they encountered were nevi, acne, and eczema, they were able to delay in-person visits for at least 3 months in 85% of their cohort, although the long-term outcomes of postponing these appointments are unknown [38]. Kazi et al [39] found that immunomodulatory and biologic therapies were more frequently prescribed with synchronous encounters, whereas antibiotics and nonretinoid acne medications were more frequently prescribed with asynchronous encounters using patient-generated photographs. This may indicate that SAF teledermatology is less appropriate for the management of complex medical dermatology than synchronous teledermatology [39]. Current data suggest that patient-submitted images are useful for managing well-established, straightforward conditions such as acne. However, more research is needed to investigate other highly relevant clinical outcomes, such as the quality of life and prevention of disease.

For clinicians referring patients to dermatology, additional considerations included the triage of patients based on their skin condition and the outcomes of triage. A group in England

conducted a pilot study for skin cancer referrals in which patients were triaged based on clinician-taken photographs [40]. They found that 43.8% of patients were allocated a clinic appointment, 20.2% of patients were booked for dermatologic surgery, and 35.1% of patients avoided a FTF visit [40]. It is conceivable that an even larger proportion of patients could avoid FTF appointments for general dermatologic concerns. For instance, Bergamo et al [41] observed that 84% of teledermatology consultations from PCPs involved diagnostic and therapeutic recommendations that avoided FTF visits [41]. Similar to research involving patient-generated images, data on the clinical outcomes of postponing or avoiding dermatology clinic visits are needed.

Inpatient Management

Unlike the outpatient setting, research on SAF teledermatology in the inpatient setting is limited to clinician-initiated images. Prior to the COVID-19 pandemic, data regarding asynchronous teledermatology for inpatient consultations were scarce. Barbieri et al [42] found that SAF teledermatology was potentially useful for triaging inpatient consultation, as teledermatologists agreed with in-person dermatologists on the need for same-day evaluation and biopsy in >90% of consultations [42].

During the COVID-19 pandemic, the integration of asynchronous teledermatology into inpatient consultations substantially increased as dermatology departments sought to maximize patient safety by minimizing unnecessary clinical exposures [35]. Consequently, some medical centers developed triage algorithms using SAF images to minimize physical contact [35,43,44]. The value of asynchronous teledermatology versus in-person evaluation for inpatient consultation depends on the medical decision in question. For instance, studies reported agreement ranging from 66% to 74% in the need to obtain a biopsy and diagnostic agreement ranging from 56% to 66.7% between teledermatologists and in-person dermatologists [42,45,46]. Gabel et al [46] observed near-perfect agreement in treatment decision but almost no agreement in next-day planning, which consisted of variations of outpatient follow-up and signing off versus continued inpatient monitoring. Keller et al [45] found that web-based and in-person dermatology consultations resulted in similar rates of change in diagnoses and treatment compared to initial decisions made by the primary team. However, agreement in the diagnosis itself (45.3%), systemic therapy (52.8%), and need for obtaining a biopsy (66%)

were somewhat discordant, indicating that these changes in decision-making may yield different clinical outcomes [45]. In addition to the dearth of research, a major limitation of the literature on SAF teledermatology for inpatient consultations is the heterogeneous measures of medical decision-making reported across different studies. Therefore, meta-analyses that examine interobserver agreement for discrete medical decisions, such as decision to biopsy or the initiation of systemic therapy, are needed.

Discussion

Principal Findings

SAF teledermatology uses electronically stored information, including patient photographs and demographic information, for clinical decision-making asynchronous to the patient encounter. The integration of SAF teledermatology into clinical practice has been increasing in recent years, especially during the COVID-19 pandemic. This narrative literature review explored 47 articles by a key element of study design—whether the images were acquired by a trained clinician or the patient, as the quality and utility of the images may vary by the clinical expertise of the photographer. In general, photographs taken by trained clinicians rather than patients are higher quality and have better and more relevant diagnostic and clinical outcomes. SAF teledermatology helped clinicians avoid unnecessary physical contact with patients in the outpatient and inpatient settings during the COVID-19 pandemic.

Future Directions

The growth and increased use of SAF teledermatology following the COVID-19 pandemic is evident. However, it remains unclear how SAF teledermatology will continue to be integrated into dermatologic practice. A cross-sectional study surveying the Association of Professors of Dermatology observed that most respondents (89%, 31/35) found the implementation of SAF images alongside video or phone calls the most feasible for teledermatology visits [47]. Of those who were most ready for teledermatology implementation, all respondents indicated they would continue to use teledermatology after the pandemic [47]. Havele et al [48] reviewed 1110 pediatric dermatology video visits and 89 SAF consultations with surveys embedded into every web-based encounter. Most respondents (76%) used parent-submitted photographs to supplement video visits, and a majority (73.4%) of clinicians who lacked photographs believe that photographs would have helped with the diagnosis [48]. Therefore, hybrid teledermatology visits using both synchronous and asynchronous communication may become more prevalent in practice [49].

Barriers to Implementation

Substantial barriers must be overcome before SAF teledermatology can be implemented into standard dermatologic care across multiple systems of practice (Figure 1). Adherence to established privacy and ethics regulations may pose substantial medicolegal risks to clinicians capturing patient photographs [50]. For this reason, clinicians should obtain proper patient consent, explain how images will be used, and delete the images from their smartphones after being uploaded

to patient charts while ensuring sufficient security in their digital communications [50]. In general, patients prefer giving verbal consent and their photographs being taken by clinic- or hospital-owned cameras [51]. EHR programs such as Epic and Cerner as well as new mobile apps allow for the secure upload of patient images to their medical charts without permanent storage on the user's device [52].

Secure apps that combine SAF images with patient communication could streamline the delivery of teledermatology care. Such apps currently exist but may be difficult to use, lack EHR integration, or incur substantial out-of-pocket costs to patients [53]. Kim et al [26] developed a SAF teledermatology consultation workflow built within an Epic-based EHR, which could simplify asynchronous dermatology consultation, especially for large health care networks with a unified EHR.

Furthermore, increased clinician workload and the lack of a definitive reimbursement model cause asynchronous teledermatology to be a substantial burden or gamble for many practices [54-56]. Currently, Medicaid reimburses clinician-initiated SAF teledermatology consultation in fewer than half of all US states, whereas Medicare only reimburses as part of telemedicine demonstration programs in Alaska and Hawaii [57]. Reimbursement for the evaluation of patient-submitted images has been proposed but not implemented by the Centers for Medicare and Medicaid Services [56]. Given that telephone-based consultation has a definitive reimbursement model that has become more flexible following the pandemic, a similar policy should be considered for SAF teledermatology services, especially those that supplement other web-based appointments [49]. Patient privacy, complex SAF teledermatology workflows, and the lack of a definitive reimbursement model are key challenges that need to be addressed with more widespread adoption of SAF teledermatology.

Limitations

This narrative literature review was limited by the sole inclusion of studies published in English that were available in PubMed and Google Scholar, which may have excluded other important studies not available in English or not indexed in these databases. Our review included both qualitative and quantitative studies; although both study types are valuable for learning about SAF teledermatology, quantitative outcomes may be more relevant and prognostic for health care systems considering the implementation of new SAF programs. Furthermore, many prospective studies included in this review involved motivated patient cohorts or referring clinicians who were equipped with thorough instructions. These conditions are often not representative of actual clinical practice and could have limited applicability to a real-life setting. Finally, many studies included in this review used patient cohorts with relatively small sample sizes (<100 subjects) and consequently reported descriptive outcomes or had wide variability in their data. More quantitative studies on the outcomes of SAF teledermatology with larger cohorts are needed.

Conclusion

SAF teledermatology has a growing role in dermatology with increasingly promising diagnostic utility and clinical outcomes over the past 2 decades. Assessing SAF teledermatology by whether images are submitted by patients or clinicians can illuminate key differences in outcomes. For instance, image quality and diagnostic concordance are generally lower and more variable with patient-submitted images, which may impact their decision-making utility. SAF teledermatology can improve the efficiency of and access to care when photographs are taken by either clinicians or patients. Only the long-term clinical outcomes of clinician-submitted images have been studied, albeit to a limited extent. Amid the COVID-19 pandemic, the

use and role of SAF teledermatology rapidly expanded in the inpatient and outpatient settings. For the outpatient setting, asynchronous teledermatology helped avoid FTF visits unless necessary, as many uncomplicated conditions could be managed remotely via images captured by patients and referring clinicians. For the inpatient setting, SAF teledermatology minimized unnecessary contact during dermatology consultations, although current studies are limited by the heterogeneity of their outcomes. Asynchronous teledermatology will likely play a greater role in the future, becoming incorporated into hybrid SAF and video teledermatology models. However, the obstacles summarized in this review should be addressed before its widespread implementation into clinical practice.

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Authors' Contributions

SWJ and MWN contributed to the conceptualization of the manuscript. SWJ and MSF contributed to the literature search. SWJ contributed to the writing and preparation of the initial draft. SWJ contributed to the visualization of the tables and figures. SWJ, MSF, JTK, and MWN contributed to the review and editing of subsequent drafts and figures.

Conflicts of Interest

None declared.

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Abbreviations

EHR: electronic health record

FTF: face-to-face

PCP: primary care physician

SAF: store-and-forward

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Original Paper

Evaluation of WhatsApp as a Platform for Tele dermatology in Botswana: Retrospective Review and Survey

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Abstract

Background: In emerging market countries in sub-Saharan Africa, access to specialty services such as dermatology is limited. Tele dermatology is an innovative solution to address this issue; however, many initiatives have been tried without sustained success. Recently, WhatsApp has been used as a store-and-forward telemedicine communication platform for consultation and education in Botswana.

Objective: This study aims to describe the utilization of WhatsApp for tele dermatology and the satisfaction levels of participating providers.

Methods: A 2-part pilot study was conducted. First, a retrospective review was performed of WhatsApp communications received by participating dermatologists in Gaborone, Botswana, from January 2016 to December 2019. Sender information, patient demographics and history, response time, diagnoses made, and follow-up recommendations were collected. Second, a 12-question cross-sectional survey was distributed to health care providers who utilized WhatsApp for tele dermatology during this period. Descriptive statistics were then performed.

Results: There were 811 communication threads over the study period. The majority (503/811, 62%) of communications were consultations from providers inquiring about a specific patient, followed by multidisciplinary care coordination communications (90/811, 11%). Our in-depth analysis focused on the former. In 323 (64%) provider consultations, dermatologists responded within 1 hour. A diagnosis was made in 274 (55%) consultations. Dermatologists gave treatment recommendations remotely in 281 (56%) consultations and recommended an in-person dermatology visit in 163 (32%). Of the 150 health care providers surveyed, 23 (15%) responded. All respondents (100%) felt that there was a need for tele dermatology and improved tele dermatology education in Botswana. Moreover, 17 (74%) respondents strongly felt that the guidance received via WhatsApp was high quality, and 22 (96%) were satisfied with WhatsApp as a platform for tele dermatology.

Conclusions: This retrospective review and survey demonstrated that WhatsApp is a quick, well-received, and sustainable method of communication between dermatologists and providers across Botswana. The app may offer a solution to the challenges providers face in accessing specialty referral systems, point-of-care education, and medical decision-making support for complex

dermatologic cases in Botswana. The information gained from this pilot study can serve as the basis for future telemedicine studies to improve the implementation of teledermatology in Botswana and other resource-limited countries.

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KEYWORDS

dermatology; teledermatology; telehealth; eHealth; mHealth; WhatsApp; developing countries; Botswana; Africa; low income; retrospective review; instant messaging

Introduction

Despite a high burden of dermatologic diseases, access to dermatologic specialty care is scarce in sub-Saharan Africa [1,2]. In Botswana, there are as few as 10 physicians per 100,000 people and even fewer dermatologists, all of whom are in large urban areas [3,4]. Currently, there are approximately 4 dermatologists practicing in the public health sector in Botswana to support a population of 2 million people. Primary care providers in Botswana have limited training in dermatology and face challenges in treating complex dermatologic conditions and successfully referring patients to specialists [5]. Additionally, coordinating care between specialties can be difficult in Botswana [6]. Thus, there is a significant need to improve the delivery of high-quality dermatologic care to remote settings by providing local health care workers with better access to dermatology expertise and education.

Teledermatology is a potential solution to address these challenges. Formal telemedicine platforms have been specifically designed to securely communicate predetermined sets of information between providers. Several have been developed and trialed in Botswana. In 2007, the Africa Teledermatology Project began providing health care providers in many sub-Saharan African countries, including Botswana, free access to a web-based platform for consultations, forum discussions, and educational materials [7]. In 2011, a partnership between the Ministry of Health of Botswana, the Botswana-UPenn Partnership (BUP), and the Orange Foundation of Botswana resulted in a multispecialty mobile telemedicine solution, including teledermatology, called “Kgonafalo” [8]. In 2015, through the Television White Space Project, several local and international partners collaborated to provide low-cost wireless broadband internet to improve telemedicine connectivity for remote clinics in Botswana [9]. However, sustained success has been difficult with these programs. The African Teledermatology Project, although still successfully running, operates primarily on a web-based platform, which can be difficult to access in remote locations. Technical challenges, such as limited desktop equipment, slow connectivity, and device malfunctions, are common. Kgonafalo utilized a specially developed mobile app, and the burden of training a constantly changing population of primary care providers was high. In addition, Kgonafalo used designated clinic mobile phones, which needed to be maintained and charged, and users needed to be comfortable using them. Most of all, these programs were difficult to implement due to loss of provider confidence and motivation to use formal telemedicine platforms in the face of multiple challenges [5,7,9].

Although formal teledermatology platforms can offer security and standardization, in low resource settings, the associated logistical and cost burdens frequently render them unfeasible or unsustainable, as previously seen in Botswana. Informal platforms are an alternative that allow the transmission of information via flexible, secure methods that can function on personal mobile phones and with lower bandwidth. Teledermatology through mobile health (mHealth) has demonstrated technical feasibility and reliability in providing care to underserved and remote populations around the world where smartphones are common, but the key to utilization is the ability to send consults within an app that is familiar to the user on their own mobile device [10-13]. mHealth was first introduced in 2009 in Botswana as a clinical education tool that was found to be effective and satisfactory among resident physicians [14]. In the past 10 years, studies have shown that mobile telemedicine systems are deemed acceptable by patients in Botswana [1] and have the potential to increase access to care across multiple specialties [5,8,15-18].

Mobile phone subscriptions have been increasing in resource-limited countries [19], and WhatsApp, a service with over 1 billion users worldwide, is the predominant form of electronic communication in Botswana [20]. In 2016, one of the authors (VW), who was working as a dermatology specialist in Botswana, noted the critical need for a sustainable method of teledermatology to connect providers across the country. In the absence of resources to develop and launch a new formal teledermatology program, she established a store-and-forward teledermatology consultation network using WhatsApp. Implementation was fast and easy because the application did not require dedicated training, specific equipment, or Wi-Fi connectivity, and most providers were already using WhatsApp for other types of communication [6].

Because WhatsApp is a relatively new platform for teledermatology, it is important to understand how physicians in Botswana are currently using it and gain user feedback to determine its feasibility, effectiveness, and potential to scale for use in other specialties. This pilot study aims to describe how the WhatsApp application is being utilized in Botswana to connect providers to dermatology expertise for patient care and education, as well as to elucidate current provider satisfaction with the platform.

Methods

Ethics Approval

This study was approved by the University of Botswana and the Botswana Health Research and Development Committee institutional review boards (HPDME 13/18/1) and was granted

a review exemption by the University of Pennsylvania IRB (835003).

Retrospective Review of WhatsApp Communications

Study Population, Setting, and Design

In the first part of the study, we conducted a retrospective review of teledermatology communications sent through WhatsApp in Botswana from January 2017 to December 2019. Messages from health care providers and patients seen within the public health care system of Botswana were sent to 2 dermatology consult mobile phones. Messages were reviewed by a full-time local dermatologist and rotating North American dermatology residents and faculty at Princess Marina Hospital (PMH) in Gaborone, Botswana. WhatsApp messages were downloaded from the mobile phones, and conversation threads found on both were identified as duplicates and removed. There was no specific record kept of which dermatologist reviewed and responded to individual messages.

Data Collection

An overview of the data extraction and categorization methods used to analyze conversation threads is summarized in [Multimedia Appendix 1](#). Each conversation thread was broadly categorized by the purpose of the communication: consultation from a provider (nondermatologist to dermatologist), consultation from a patient (patient to dermatologist), remote patient management (inquiries regarding long-term management for known diagnosis), patient follow-up (provider message regarding patient already known to dermatologist), teletriage (requiring urgent dermatology appointment), multidisciplinary care coordination (organizing patient care activities between 2 or more providers), provider question (unrelated to a specific patient), and incomplete communication (lack of response from dermatologist, an abrupt stop in the conversation, or conversation continued outside of WhatsApp). Other purposes of communication were excluded. Sender information (phone number, profession, and location) was collected from all communications if available.

Further data collection was only performed on the consultations received from a provider. We extracted data into categories that were considered to be most important to patient care in Botswana, including patient demographics, history provided, photograph parameters, response time, diagnosis, and outcome of consultation. Patient age, sex, and HIV status were recorded if provided. The extent of a history of present illness (HPI) shared by the nondermatologist provider was based on a point system, with 1 point given for each of the following: description of the lesion, location on the body, symptoms reported, timing of onset, change in appearance over time, aggravating or alleviating factors, prior treatments performed, and pertinent lab or imaging results.

Photographs received with consultations were also reviewed. Two authors (TW and AF) with experience reviewing teledermatology consultation photos in Botswana developed a subjective grading system that rated photos as low, medium, or high quality based on criteria of image resolution, lighting, and content (whether photos captured relevant areas of the body). To standardize grading, photos were reviewed by 2 authors

(VW and AF) until a consistent agreement on grading was achieved. After standardization was achieved, each photo was graded by 1 author. The file size (kB) of photographs was also recorded. [Multimedia Appendix 1](#) provides more details of the process used to grade photographs.

Response times from dermatology consultants was stratified (0-60 minutes, 1-6 hours, 6-12 hours, 12-24 hours, 24-48 hours, and >48 hours) based on both the time from initial message sent to initial response and initial message sent to final diagnosis or recommendation. Dermatologists provided no diagnosis, a single diagnosis, multiple diagnoses, and/or differential diagnoses in response to consultations from providers. All diagnoses, including those that were differentials, were included in the overall analysis. Diagnoses were classified into the major categories of inflammatory disorders, infection, neoplasm, diseases of vasculature, and other diagnoses. Consultation outcomes were based on the dermatologist's recommendation and divided into the following categories: advice for local management (when treatment recommendations were provided remotely), referral to see a dermatologist, referral to see a different specialist, or other recommendation. We recorded whether dermatologists provided education to providers (clinical information in addition to a diagnosis and treatment plan).

Statistical Analysis

Descriptive statistics were used to broadly categorize the conversation threads and demographic and clinical data provided in the consultations.

Satisfaction Survey of Providers Using WhatsApp for Teledermatology

Study Population, Setting, and Design

In the second part of the study, we conducted a cross-sectional survey of health care providers in Botswana who used WhatsApp for teledermatology from January 2016 to December 2019.

Data Collection

A research electronic data capture (REDCap) survey was distributed via WhatsApp, and responses were kept anonymous. The target population was a convenience sample of providers that used the platform for consultations. Informed consent was obtained from all participants. This was a voluntary, open survey that consisted of 12 questions aimed at evaluating users' satisfaction and experience with the platform in terms of technical quality, perceived effectiveness and usefulness, privacy and security practices, and suggestions for improvements ([Multimedia Appendix 2](#)). We developed a novel survey that was not based on an existing validated survey instrument to evaluate for factors most pertinent within the local context. The first 6 questions used a Likert scale to evaluate the overall value of WhatsApp as a teledermatology tool. The subsequent 6 questions were multiple-choice questions regarding specific aspects of the platform as well as user practices. Survey questions were developed in REDCap by dermatology and informatics faculty at the University of Pennsylvania, Ministry of Health and Wellness of Botswana, and the University of

Botswana, who had experience with the local health care system's needs and limitations.

Statistical Analysis

The frequency of responses to survey questions were recorded and reported, and common themes in areas for improvement were identified.

Results

Retrospective Review of WhatsApp Communications

From January 2017 to December 2019, there were a total of 811 conversation threads, with 102 threads in 2017, 350 in 2018, and 324 in 2019. There were 35 threads with a missing date

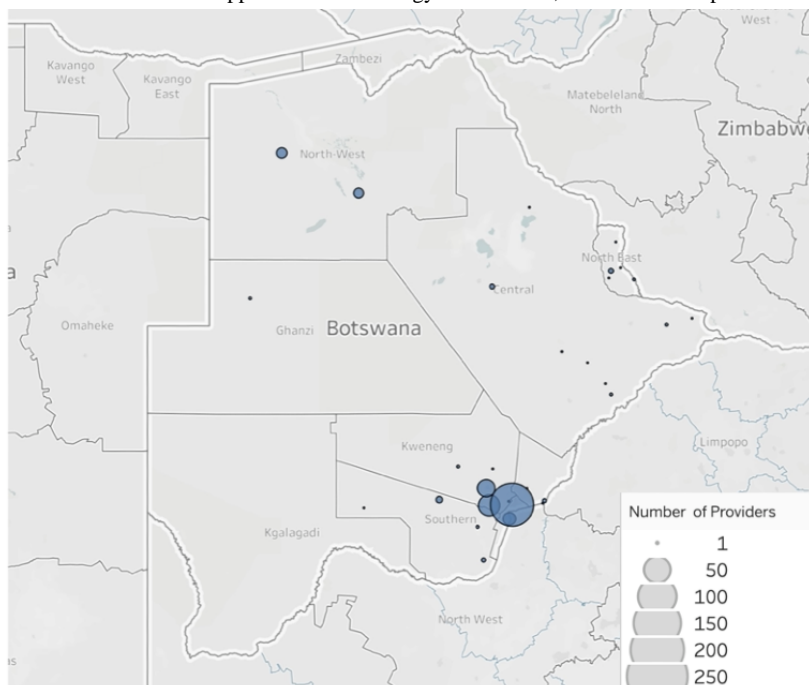
stamp that were also included in the analysis. Approximately 150 senders were identified based on unique phone numbers and names in the phone contact list. An exact number of senders could not be confirmed due to inconsistencies in the way contact information was saved in each mobile phone.

The most common (503/811, 62%) purpose of communication was a consultation from a provider, as seen in the conversation threads, followed by multidisciplinary care coordination (23/811, 11%) (Table 1). The profession of the provider was stated in 44% (355/811) of the conversation threads, and 90% (320/355) were physicians. The provider's location was stated in 58% (473/811) of the threads. There was wide variation in locations across Botswana as well as other sub-Saharan African countries (Figure 1).

Table 1. Categories of communication between dermatologists and nondermatologist providers according to WhatsApp communication threads (N=811).

Purpose of communication	Communication threads, n (%)
Consult from provider	503 (62)
Consult from patient	23 (3)
Remote patient management	7 (1)
Patient follow-up	55 (7)
Teletriage	44 (5)
Multidisciplinary care coordination	90 (11)
Provider question	23 (3)
Incomplete consult	66 (8)

Figure 1. Locations of providers that utilized WhatsApp for teledermatology in Botswana, with number of providers in each location.



Our in-depth analysis focused on the 503 WhatsApp consultations from nondermatologist providers (Table 2). An example of a consultation is provided in Figure 2. Providers gave an average of 3.1 out of 8 possible points of HPI based on our point system. Patient age was provided in 76% (380/503) of the consultations, sex in 76% (383/503), and HIV status in 47%

(234/503). The majority (477/503, 95%) provided a photo. Responding dermatologists asked clarifying questions in 40% (200/503) of consults. The average patient consulted on was 30.5 years old (ranging 8 days to 84 years), in which 59% (226/503) were female, 41% (157/503) were male, and 38% (89/503) were HIV positive.

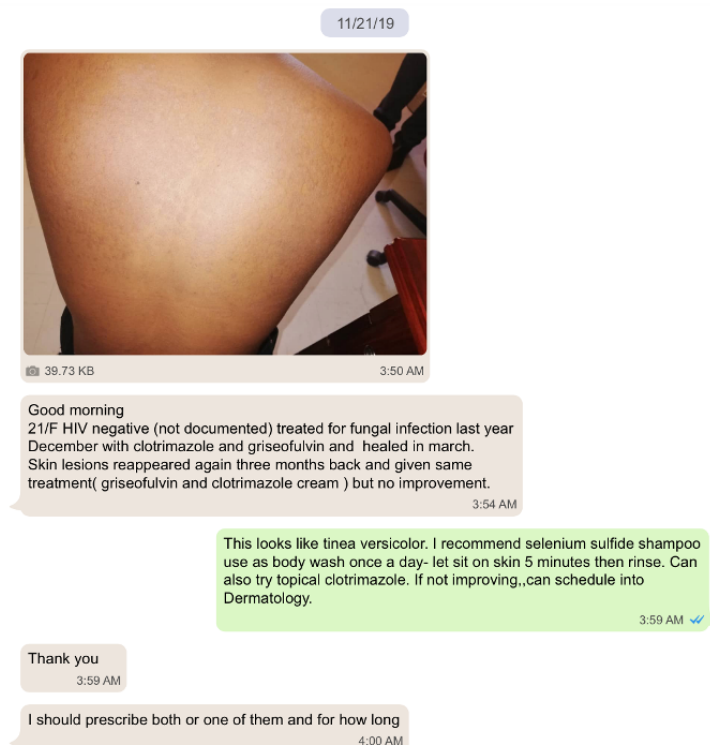
Table 2. Format of consultations sent by nondermatologist providers (N=503).

Measures	Consultations
Age provided, n (%)	380 (76)
Sex provided, n (%)	383 (76)
HPI ^a provided, mean (SD) ^b	3.1 (1.6)
HIV status provided, n (%)	234 (47)
Photo provided, n (%)	477 (95)
Photo subjective grade^c, n (%)	
Low	101 (20)
Medium	198 (39)
High	178 (35)
Photo file size, n (%)	
<50 Kb	173 (34)
50-100 kB	214 (42)
100-150 kB	52 (10)
>150 kB	37 (7)

^aHPI: History of present illness.

^bHPI provided in the consultation was graded on a point system, with 1 point given for each of the following: description of the lesion, location on the body, timing of onset, change in appearance over time, aggravating and alleviating factors, prior treatments performed, symptoms reported, and pertinent lab or imaging results.

^cSubjective photograph quality was determined based on a grading system in which the criteria were image resolution, lighting, and whether relevant areas of the body were captured. Photos were graded on a scale of low, medium, or high quality based on the number of quality criteria met ([Multimedia Appendix 1](#)).

Figure 2. Example of a consultation sent from a nondermatologist provider to a dermatologist.

Dermatologists responded to the provider within 1 hour in 64% (323/503) of consultations and provided the final diagnosis or recommendation in 54% (272/503) ([Table 3](#)). In over half (274/503, 54%) of consultations, a single diagnosis or multiple

diagnoses were made. A differential diagnosis was provided in 32% (159/503) of consultations. Dermatologists recommended management to be given by the local provider in 56% (281/503) of consultations, and in 32% (163/503), patients were

recommended to schedule an in-person dermatology visit. Additional education was provided by dermatologists in 28% (140/503) of consultations.

Dermatologists provided 224 unique diagnoses out of a total of 704 diagnoses made. The most common were eczema, contact

dermatitis, and warts ([Multimedia Appendix 3](#)). In broad categories, 48% (333/704) were categorized as inflammatory diagnoses, 29% (203/704) infectious, 10% (69/704) neoplastic, 3% (21/704) diseases of vasculature, and 19% (73/704) other.

Table 3. Outcomes of consultations sent by nondermatologist providers (N=503).

Measures	Consultations, n (%)
Time to initial response	
0-59 minutes	323 (64)
1-6 hours	120 (24)
6-12 hours	35 (7)
12-24 hours	8 (2)
24-48 hours	6 (1)
>48 hours	11 (2)
Time to final diagnosis or recommendation	
0-59 minutes	272 (54)
1-6 hours	144 (29)
6-12 hours	35 (7)
12-24 hours	13 (3)
24-48 hours	10 (2)
>48 hours	14 (3)
No final diagnosis or recommendation	15 (3)
Diagnosis provided^a	
Single diagnosis	259 (52)
Multiple diagnoses	15 (3)
No diagnosis made	229 (46)
Differential diagnosis provided ^a	159 (32)
Dermatologist recommendations	
Local management	281 (56)
Dermatology referral	163 (32)
Referral to other specialist	15 (3)
Other	44 (9)
Education provided	140 (28)

^aEach patient could have single or multiple conditions presented by the consulting provider. Each of these conditions was considered separately by the evaluating dermatologist. The evaluating dermatologist could provide a single diagnosis, multiple diagnoses (at least 2), no diagnosis, and/or a differential diagnosis for any condition they determined was present.

Satisfaction Survey of Providers Using WhatsApp for Tele dermatology

A survey was sent out to approximately 150 health care providers, of which 15% (23/150) completed the survey ([Multimedia Appendix 2](#)). Demographics of survey respondents are shown in [Multimedia Appendix 4](#). All respondents felt that there was a need for tele dermatology, improved tele dermatology education, and improved communication between dermatologists and other health care providers in Botswana ([Figure 3](#)). Most respondents (20/23, 87%) strongly agreed that they needed help

with diagnosing and managing skin conditions, 83% (19/23) agreed that using WhatsApp for tele dermatology enhanced their dermatology skills, and 87% (20/23) felt it improved their ability to manage patients in their own clinic to avoid referral. Most respondents (17/23, 74%) strongly felt that guidance received via WhatsApp was of high quality, and 96% (22/23) were satisfied with WhatsApp as a platform for tele dermatology ([Figure 3](#)). The highest-rated features of using WhatsApp as a tele dermatology platform included the ease of sending consults (21/23, 91%), having previous knowledge on how to use the

application (20/23, 87%), and ease of asking follow-up questions (19/23, 83%) (Table 4).

In terms of privacy and security, only two-thirds (15/23, 65%) of respondents reported always obtaining consent from patients for photos to be sent via teledermatology. Of those who obtained consent, all obtained verbal instead of written consent. Nearly all respondents used a personal phone (21/23, 91%) or camera (1/23, 4%). A majority (14/23, 61%) kept these photos on a password protected device, but nearly one-third (9/23, 39%) did not or only occasionally did. Most respondents (19/23, 83%) were not concerned about privacy or security issues while using

WhatsApp for teledermatology. Concerns reported included the possibility of hacking, forwarding photos, and inappropriate access by third parties (Table 4).

When asked about areas of improvement, respondents shared issues regarding the timing of responses, availability of consultants, and difficulty keeping case discussions organized when multiple separate patient consults were sent within 1 text thread. Another provider expressed concern about patients being able to obtain an in-person follow-up by a dermatologist when needed.

Figure 3. Responses to the Provider Satisfaction Survey questions assessing the overall utility of WhatsApp as a teledermatology platform.

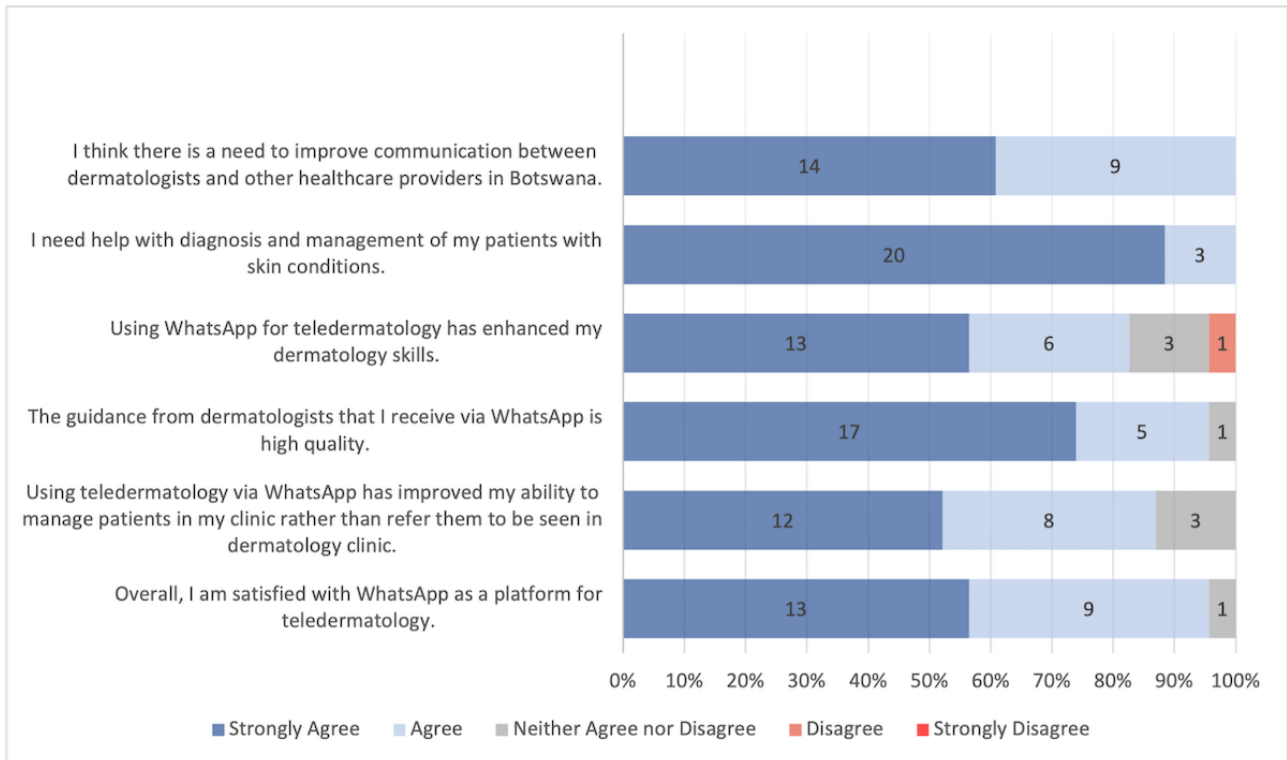


Table 4. Responses to the Provider Satisfaction Survey questions assessing specific features of WhatsApp as a teledermatology platform and patient data safety practices (N=23).

Questions	Responses, n (%)
Which of the following features do you like about using WhatsApp for teledermatology? (Select all that apply)	
Easy to send consults	21 (91)
I already have and know how to use the application	20 (87)
Easy to ask follow-up questions	19 (83)
Fast response times	14 (61)
Doesn't require a computer with Internet	10 (44)
Easy to get patients urgently scheduled with dermatology clinic	11 (48)
Do you obtain consent from patients for photos to be transmitted by teledermatology?	
Always	15 (65)
Almost always	6 (26)
Often	1 (4)
Never	1 (4)
How do you obtain consent from patients?	
Verbal	23 (100)
Written	0 (0)
What device do you use to send consults?	
Personal phone	21 (91)
Work phone	3 (13)
Personal camera	1 (4)
Work camera	0 (0)
Other	0 (0)
Do you keep patient photos on a password-protected device?	
Yes	14 (61)
No	7 (30)
Sometimes	2 (9)
Do you have concerns about the privacy and/or security of using WhatsApp for teledermatology?	
No	19 (83)
Yes	4 (17)

Discussion

Principal Findings

This pilot study describes the use of WhatsApp, a popular text messaging app, as an informal teledermatology platform for consultation and education in Botswana and demonstrates that WhatsApp provides a rapid and well-received method of communication between dermatologists and other health care providers.

In our study, the most common use of WhatsApp by health care providers was to consult a dermatologist about a specific patient. Our results indicate that WhatsApp facilitates rapid discussion of dermatology cases, as dermatologists responded within 1 hour for the majority of consults. In addition, group messaging was utilized to provide a platform for simultaneous communication among a team of care providers to facilitate

multidisciplinary care coordination, which has been a particular challenge in Botswana [6]. Overall, our study demonstrated that WhatsApp is being used as a direct line of communication between providers to promote care coordination, provide triage advice for life-threatening conditions, disseminate dermatology education, and allow for direct patient care when appropriate. This reinforces the previous conclusions of Littman-Quinn et al [5] that mHealth tools may offer a solution for improving access to specialty care in resource-limited settings by increasing access to specialty referrals, point-of-care information, and medical decision-making support for complex dermatologic cases.

The sustainability of teledermatology platforms has been a historical challenge in resource-limited countries [21]. Compared to previous formal telemedicine platforms that have not been successful in the long term in Botswana, WhatsApp has several

attributes that increase its potential for sustainability: ease of use, free access on personal mobile devices, and no dedicated funding required to maintain it as a telemedicine platform [5,22]. To date, WhatsApp has been used for over 4 years as a teledermatology tool at Princess Marina Hospital in Botswana and has been increasing in popularity since its inception [5,22]. Around 90% of survey respondents indicated they valued the simplicity and familiarity of the application. In another low-resource areas in the Middle East, a survey illustrated a similarly high satisfaction rate with mHealth-based teledermatology, which was also attributed in part to feasibility [23].

One potential drawback of informal platforms such as WhatsApp is the lack of standardized consultation format, which allows for free-text submission of consults that may be incomplete or contain an inadequate amount of information. The ability to have real-time conversational exchanges can help overcome the lack of structured consults, though this can cause inefficiency. In this study, dermatologists asked clarifying questions in nearly 40% of the consultations. Regarding photo quality, only 20% of consults included photos that were considered low quality in our subjective assessment, primarily due to user errors such as poor lighting or blurriness rather than low resolution. Notably, the subjective rating of photographs did not always correlate with file size, suggesting that high quality photos could be obtained with low-tech mobile cameras. Future studies using validated methods to assess photo quality are needed to further explore this issue.

In this study, dermatologists were able to make a wide variety of skin diagnoses in over half of the consultations, indicating that the history and quality of photos in WhatsApp consultations could adequately support remote evaluation and diagnosis. Knowing whether telemedicine diagnoses are accurate is essential when considering the utility of providing or upscaling such services; however, we were unable to assess diagnostic accuracy in this small pilot study. Some studies have indicated that diagnoses made by teledermatology can be reliable and accurate [24], but data are lacking for teledermatology on mobile devices and in settings like Botswana [18]. In our opinion, common conditions like eczema, acne, and herpes simplex virus are often simple to diagnose via teledermatology and can be managed remotely by local providers. This can save time and costs for patients, providers, and the health care system. Moreover, using teledermatology for serious and life-threatening conditions, such as the 14 cases of Stevens Johnson Syndrome identified in this study, allows for same-day triaging to appropriate care that could save lives.

WhatsApp facilitated remote management in over half of the consultations in our study, reducing the need for an in-person consultation and potentially reducing the travel and cost burdens to patients and the health care system. Patients and providers were distributed widely across Botswana, and WhatsApp was able to successfully connect patients and providers across large distances, reaching urban and rural areas. Prior research has also shown that teledermatology can help decrease unnecessary health care spending and improve allocation of resources by reducing unnecessary referrals and outpatient visits [25]. Additionally, by reducing the number of patients that need to

be seen in person, WhatsApp teledermatology consults have the potential to increase access to care for other patients with more severe skin conditions to be seen in dermatology clinics [26].

WhatsApp also has the potential to be used for provider education. In about one-third of consultations, the dermatologist provided education to complement management recommendations. Education is particularly valuable in resource-limited settings, where providers often lack access to clinical educational resources to assist in point-of-care decisions [27]. One-on-one, case-based education may help to empower providers to manage dermatologic conditions independently; however, WhatsApp has limitations when it comes to disseminating information broadly, which is important for education on a health systems level.

Our survey results showed that WhatsApp is a well-received and valuable resource for nondermatology providers. All but 1 respondent were satisfied with WhatsApp as a teledermatology platform, and many reported that it improved the quality of care they delivered. Respondents liked the familiarity of WhatsApp, which is consistent with WhatsApp being the predominant form of mobile communication in Botswana [20]. Other studies examining teledermatology and the use of mobile-health platforms in low-resource settings have shown similarly high levels of provider satisfaction [5,23,28,29].

When considering telemedicine, the privacy and security of shared patient information is extremely important. In teledermatology, many consultations include protected health information and photos of patients' faces or sensitive body areas [5,6]. Most respondents in this study reported little to no concern about the security of images obtained and sent, and WhatsApp has multiple features to increase security to message transmission such as end-to-end encryption [30]. However, most providers took images on their personal phones. Nearly one-third stored images on devices that were not password protected, and almost one-third occasionally or rarely obtained patient consent to take photos to send to other providers. It has been reported that the sharing of medical photography between physicians on personal smartphones is generally accepted by patients, who may feel that the benefit of receiving timely, quality medical care outweighs the risks of data security from texting or emailing between physicians [31]. However, patient expectations may vary, and physicians should follow local laws and regulations regarding patient privacy. All telemedicine systems, and indeed all medical systems, carry some risk for patient privacy breaches, and some countries have additional guidelines to prevent accidental exposure of confidential information [22].

Limitations

Our study has several limitations. Data collection was a manual process with only 1 author reading each conversation thread, increasing the risk for errors and subjectivity, particularly in terms of grading photos. Due to the retrospective nature of the study, the heterogeneity of information provided, and the nature of downloading WhatsApp messages, we were unable to accurately calculate the number of users and all patient demographics. In addition, the number of patients electronically visited was not able to be assessed given the lack of a medical

record number or chart linked to each informal teledermatology consult. As previously discussed, this study did not measure accuracy of diagnoses made via WhatsApp, which would be required to measure the overall effectiveness of the platform for teledermatology. The survey was a subjective measurement of the perceived value of teledermatology, not based on a previously validated or reliable survey instrument. A limited number of questions were used to avoid participant burden and survey fatigue. Due to low response rate, survey results may not represent the opinions of all providers using WhatsApp for teledermatology. Reasons for the low response rate are unknown, but they may include the distribution of surveys by cellular messaging, the lack of incentive for participating, and that some providers messaged were no longer participating in WhatsApp teledermatology. Additionally, study findings may not be generalizable to other resource-limited settings due to various regional differences. Despite these limitations, this pilot study serves as an important baseline to inform future investigations of WhatsApp to include diagnostic accuracy, patient acceptability, health outcomes, and the development of standardized guidelines for provider exchange.

Conclusions

Access to dermatology expertise remains a critically limited resource in Botswana. This study shows that there has been consistent and well-received use of WhatsApp for teledermatology in Botswana without dedicated funding, training, or equipment. The platform demonstrates a potential to support a variety of clinical purposes, such as patient consultations, triage and referral, multidisciplinary care coordination and point-of-care education. High satisfaction levels and an improvement in the ability to diagnose and manage a range of dermatologic conditions were evidenced by WhatsApp user feedback. Drawbacks identified include a lack of structured consultation format, potential security risks for patient information, and the inability to integrate consult information into a patient's record. Despite these drawbacks, convenient, informal teledermatology platforms such as WhatsApp show promise in overcoming the logistical and sustainability challenges that have hampered teledermatology efforts in resource-limited settings. Further studies are needed to assess the effectiveness of WhatsApp and evaluate patient acceptability. The information gained from this study can serve as a baseline for future telemedicine studies and to inform the design and implementation of teledermatology in Botswana and other resource-limited countries.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Summary of data extraction and categorization methods used for analysis of WhatsApp communication threads.

[[DOCX File , 17 KB - derma_v5i3e35254_app1.docx](#)]

Multimedia Appendix 2

Provider Satisfaction Survey.

[[DOCX File , 15 KB - derma_v5i3e35254_app2.docx](#)]

Multimedia Appendix 3

Top ten most common conditions diagnosed by dermatologists via WhatsApp. Evaluating dermatologists made a total of 704 diagnoses and differential diagnoses which included 224 unique conditions. The numerical value and percentages in the table represent a portion of the 704 diagnoses and differential diagnoses.

[[DOCX File , 71 KB - derma_v5i3e35254_app3.docx](#)]

Multimedia Appendix 4

Demographics of survey respondents.

[[DOCX File , 13 KB - derma_v5i3e35254_app4.docx](#)]

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Abbreviations

BUP: Botswana-UPenn Partnership
HPI: history of present illness
IRB: institutional review board
mHealth: mobile health
PMH: Princess Marina Hospital
REDCap: research electronic data capture

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Original Paper

To Refer or Not to Refer in Teledermoscopy: Retrospective Study

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Abstract

Background: Challenges remain for general practitioners (GPs) in diagnosing (pre)malignant and benign skin lesions. Teledermoscopy (TDsc) supports GPs in diagnosing these skin lesions guided by teledermatologists' (TDs) diagnosis and advice and prevents unnecessary referrals to dermatology care. However, the impact of the availability of TDsc on GPs' self-reported referral decisions to dermatology care before and after the TDsc consultation is unknown.

Objective: The objective of this study is to assess and compare the initial self-reported referral decisions of GPs before TDsc versus their final self-reported referral decisions after TDsc for skin lesions diagnosed by the TD as (pre)malignant or benign.

Methods: TDsc consultations requested by GPs in daily practice between July 2015 and June 2020 with a TD assessment and diagnosis were extracted from a nationwide Dutch telemedicine database. Based on GP self-administered questions, the GPs' referral decisions before and their final referral decision after TDsc consultation were assessed for (pre)malignant and benign TD diagnoses.

Results: GP self-administered questions and TD diagnoses were evaluated for 6364 TDsc consultations (9.3% malignant, 8.8% premalignant, and 81.9% benign skin lesions). In half of the TDsc consultations, GPs adjusted their initial referral decision after TD advice and TD diagnosis. Initially, GPs did not have the intention to refer 67 (56.8%) of 118 patients with a malignant TD diagnosis and 26 (16.0%) of 162 patients with a premalignant TD diagnosis but then decided to refer these patients after the TDsc consultation. Furthermore, GPs adjusted their decision from referral to nonreferral for 2534 (74.9%) benign skin lesions (including 676 seborrheic keratosis and 131 vascular lesions).

Conclusions: GPs adjusted their referral decision in 52% (n=3306) of the TDsc consultations after the TD assessment. The availability of TDsc is thus of added value and assists GPs in their (non)referral for patients with skin lesions to dermatology care. TDsc resulted in referrals of patients with (pre)malignant skin lesions that GPs would not have referred directly to the dermatologist. TDsc also led to a reduction of unnecessary referrals of patients with low complex benign skin lesions (eg, seborrheic keratosis and vascular lesions).

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KEYWORDS

teledermoscopy; dermoscopy; telemedicine; telehealth; triage; general practitioner; GP; general practice; family doctor; family physician; unnecessary referrals; refer; referral; skin; lesion; specialist; physician communication; diagnostic; interprofessional; diagnose; diagnosis; dermatology; dermatologist

Introduction

In the Netherlands, patients that are concerned about their skin lesion visit their general practitioner (GP) for advice. GPs assess the skin lesions and decide if a wait-and-see policy is justified, if they can manage the skin condition themselves in their practice, or if the patient should be referred to a dermatologist. In this way, GPs serve as gatekeepers and play a key role in deciding whether a patient is referred to Dutch dermatology care. However, GPs seem to find distinguishing between benign and malignant skin lesions a difficult task [1,2]. As a result, GPs frequently refer patients with suspicious skin lesions to a dermatologist that turn out to be benign (eg, seborrheic keratosis, vascular lesions, and benign nevus) [1-4]. These mild benign skin conditions can be managed by the GP in the primary care setting, and no clinical or surgical dermatological intervention is required [1,2]. Teledermoscopy (TDsc) can provide diagnostic support to GPs to accurately triage people with suspicious skin lesions [5-8]. With TDsc, more urgent cases can be correctly referred to a dermatologist, while unnecessary referrals of people with nonsuspicious skin lesions who can be managed in primary care are avoided [5-11].

In general, previous TDsc evaluation studies in primary care settings included all eligible patients with suspicious (pigmented) skin lesions, patients who GPs regularly intend to refer, or patients who were already referred to a hospital or lesion clinic [5-7,9-11]. In addition, these previous TDsc studies were often carried out in a study setting where the feasibility of TDsc was examined with a simulated TDsc service that was not yet integrated into GP daily practice. Furthermore, in some of these TDsc studies, the GP did not act as a gatekeeper, the referral decision was made by a (tele)dermatologist and not by a GP, or the photos of the skin lesions were not acquired by the GP themselves but, for example, by a trained nurse (also called a melanographer) [6-11].

In the Netherlands, TDsc has been integrated into GP practices nationwide since 2009 by a Dutch telemedicine provider (Ksyos) and is fully reimbursed by Dutch health insurance companies [12]. The Ksyos TDsc service is unique compared to other worldwide TDsc services in primary care because this service (1) is implemented in GP general practice, (2) asks GPs to enter their initial referral decision in the Ksyos system at the start of a TDsc consultation request, and (3) asks GPs to enter their final referral decision in the system after receiving the digital assessment of the teledermatologist (TD) based on the overview, detailed, and dermoscopic images. Our previously performed TDsc evaluation in Dutch GP practices in the same context and the same Dutch TDsc system showed that the GPs adjusted their referral decision after the TD assessment in 3722 (53.3%) of the 6977 TDsc consultations [13].

Previous TDsc studies in other settings investigated common TD-provided teliagnoses and the percentage of patients for whom, due to TDsc, a physical referral to a dermatologist could be avoided [5-11]. However, these studies did not focus on patients who would initially not have been referred by the GP without the availability of TDsc. Nor did they aim to assess whether the GP's initial decision to refer or not refer a patient

before the TDsc consultation changed after the TD assessment for skin lesions diagnosed by the TD as malignant, premalignant, or benign.

Therefore, for these diagnosis groups, the impact of the availability of TDsc on the GPs' referral decisions to dermatology care is still unknown. Therefore, this study assessed and compared GPs' self-reported initial referral decisions before TDsc with their final referral decisions after TDsc for (pre)malignant and benign TD-diagnosed skin lesions.

Methods

Setting and TDsc Process Description

In the Ksyos-secured TDsc digital health record system, a GP starts the TDsc process with a standardized consultation request and uploads the obtained (detailed, overview, dermoscopic) images of a patient's skin lesion. After a GP has filled in patient information, such as year of birth, sex, prehistory of skin cancer, structured anamnesis, optional provisional diagnosis, and additional notes, the GP sends the TDsc request to a TD for review. The TD then provides a primary diagnosis (a mandatory and an optional differential diagnosis) in a text entry field and referral recommendations, which may include advice for the GP on the patient management plan.

Further, a GP is asked to answer 2 similar nonmandatory self-administered questions: (1) "Would you have referred this patient if TDsc was not available?" and (2) "Are you still referring this patient to the dermatologist?". These questions, which are embedded in the Ksyos system by default, retrieve information about (1) the GP's initial decision to refer a patient to a dermatologist (Yes, No) when sending the TDsc consultation request to a TD and (2) the GP's final referral decision (Yes, No) at the time of closing the TDsc consultation after the TD assessment.

As of July 2015, the Ksyos system generates an ICD-10 (International Classification of Diseases, 10th revision) [14] code by which diagnoses provided by TDs in TDsc consultations are automatically classified. Instead of describing the primary diagnosis in a free text entry field, TDs can also choose 1 of 3 icon buttons; no diagnosis (ICD-10 code: R69), no abnormalities (ICD-10 code: R68.8), or nonassessable (-).

Ethical Considerations

No ethical approval was required to evaluate the number of TDsc consultations, since all GPs gave permission through a contract with Ksyos to monitor TDsc quality with these self-administered questions.

Study Design

For this retrospective database study, TDsc consultations requested by GPs between July 2015 and June 2020 were included in the data analysis. Next, consultations with missing values were excluded. Missing values in the database were defined as a TD report of "no diagnosis" (R69), "no abnormalities" (R68.8), or "nonassessable" (-), or if a GP had not answered both self-administered questions. Data acquired included (1) answers to the GP self-administered questions on referral of a patient to a dermatologist and (2) diagnosis provided

by TD during the TDsc consultation. Optional differential diagnoses provided by the TD were omitted from this study. Types of cameras or digital dermoscope used to obtain the images were unknown.

The GP self-administered questions were used to define whether the GPs had or had not adjusted their initial decision to refer a patient to a dermatologist after reviewing the advice and diagnosis of the TD.

In this study, 3 diagnosis groups were defined based on the TD diagnoses and the corresponding ICD-10 codes: malignant, premalignant, and benign. The histopathology and face-to-face diagnoses were not available in our study. Malignant skin lesions included all malignant neoplasms (ICD-10 codes C00-C97) such as melanoma, basal cell carcinoma, and squamous cell carcinoma. Premalignant skin lesions were defined as a separate group and included in situ neoplasms (ICD-10 codes D00-D09), other specified epidermal thickening (ICD-10 code L85.8; eg, keratoacanthomas), and actinic keratosis (ICD-10 code L57.0). Benign skin lesions included the remaining ICD-10 diagnoses. In this group, we specifically focused on seborrheic keratosis (ICD-10 code L82) and vascular lesions (ICD-10 codes D18, I78.1). For each diagnosis group, the GP self-reported initial and final referral decisions were analyzed.

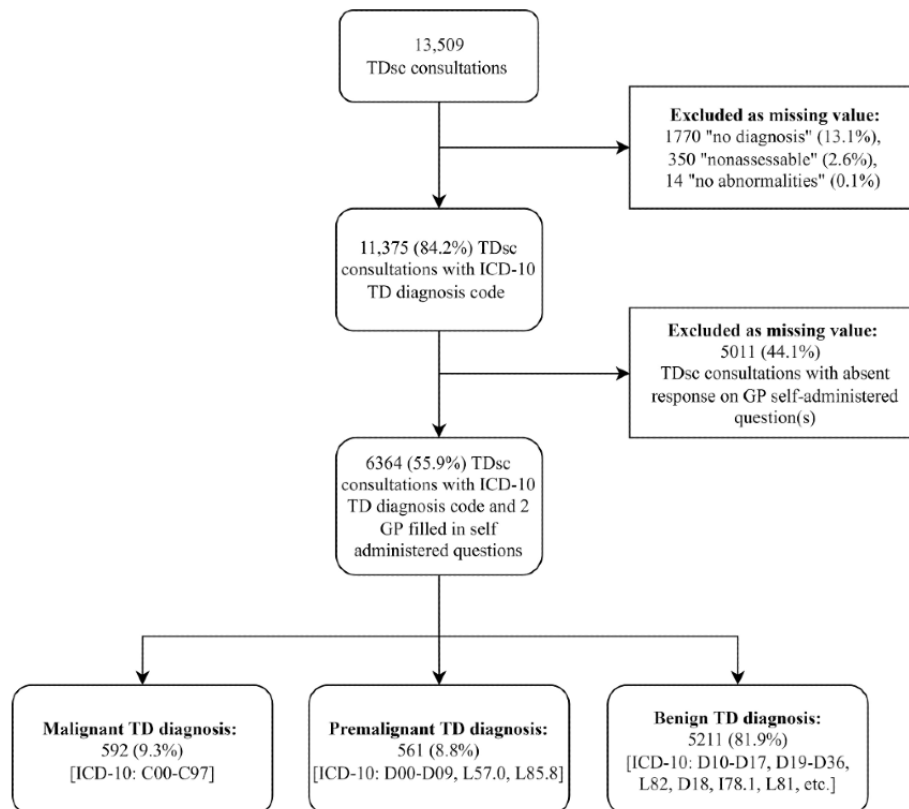
Results

Overall Cohort

In total, 13,509 TDsc consultations requested by 1185 GPs between July 2015 and June 2020 were provided with a diagnosis by 140 TDs. Of these, 1770 (13.1%) were assessed by the TD as “no diagnosis,” 14 (0.1%) as “no abnormalities,” and 350 (2.6%) as “nonassessable.” Moreover, 5011 (44.1%) TDsc consultations had an absent response on the GP self-administered question(s) and were therefore excluded as a missing value from the data set (Figure 1). For 6364 (55.9%) of the 11,375 TDsc consultations with an ICD-10 TD diagnosis code, both nonmandatory self-administered questions were answered by the GP. According to the TD diagnosis, this consisted of 592 (9.3%) skin lesions in the malignant diagnosis group, 561 (8.8%) in the premalignant diagnosis group, and 5211 (81.9%) in the benign diagnosis group. Overall, benign skin lesions were the most frequently reported diagnosis by the TDs.

Among the group of malignant diagnoses, the most common were basal and squamous cell carcinoma (n=415, 70.1%) followed by malignant melanoma (n=172, 29.1%). The most commonly provided diagnosis in the premalignant diagnosis group was actinic keratosis (ICD-10 code L57.0; n=434, 77.4%). Among the group of benign diagnoses, the most common was melanocytic nevus (ICD-10 code D22; n=2571, 49.3%), followed by seborrheic keratosis (n=1221, 23.4%).

Figure 1. Flowchart of teledermoscopy (TDsc) consultations requested by general practitioners (GPs) between July 2015 and June 2020 as included in our study. ICD-10: International Classification of Diseases, 10th revision; TD: tele dermatologist.



GPs' Referral Decision Based on Self-Administered Questions

In 3306 (51.9%) TDsc consultations, the GPs adjusted their referral decision (Yes-No, No-Yes) after the TD assessment (Table 1). For the malignant diagnosis group, GPs indicated that they would initially not have referred 118 (19.9%) patients without TDsc. For 67 (56.8%) of these 118 patients with a malignant TD diagnosis, the GPs adjusted their initial referral decision and referred the patient after TDsc consultation.

In the premalignant diagnosis group, the GPs indicated that they would not have referred for 162 (28.9%) patients without TDsc. For 26 (16.0%) of these 162 patients with a premalignant TD

diagnosis, the GPs changed their decision from nonreferral to referral.

In the benign diagnosis group, 3384 (64.9%) patients with benign skin lesions, of which 784 (64.2%) had seborrheic keratosis and 163 (70.6%) had vascular lesions, would have been referred by the GP without the availability of TDsc. The TD-provided benign diagnoses resulted in a change of the GPs' decision from referral to nonreferral for 2534 (74.9%) patients. More specifically, GPs adjusted their referral decision to nonreferral after the TD assessment for 676 (86.2%) patients with a seborrheic keratosis TD diagnosis and 131 (80.4%) patients with a vascular lesion TD diagnosis. In addition, the group of "other benign skin lesions" included benign nevi as well as ICD-10 codes for eczema and insect bites.

Table 1. Number of teledermatologists (TD) diagnoses for the general practitioner (GP) self-administered questions.

Self-administered questions	Malignant skin lesions (N=592), n (%)	Premalignant skin lesions (N=561), n (%)	Benign skin lesions, n (%)				Total TDsc ^a consultations (N=6364), n (%)
			Seborrheic keratosis (N=1221)	Vascular lesions (N=231)	Other benign skin lesions (N=3759)	Total benign skin lesions (N=5211)	
Q1^b=Yes	474 (80.1)	399 (71.1)	784 (64.2)	163 (70.6)	2437 (64.8)	3384 (64.9)	4257 (66.9)
Q2 ^c =Yes	353 (74.5)	122 (30.6)	108 (13.8)	32 (19.6)	710 (29.1)	850 (25.1)	1325 (31.1)
Q2=No	121 (25.5)	277 (69.4)	676 (86.2)	131 (80.4)	1727 (70.9)	2534 (74.9)	2932 (68.9)
Q1=No	118 (19.9)	162 (28.9)	437 (35.8)	68 (29.4)	1322 (35.2)	1827 (35.1)	2107 (33.1)
Q2=Yes	67 (56.8)	26 (16.0)	36 (8.2)	9 (13.2)	236 (17.9)	281 (15.4)	374 (17.8)
Q2=No	51 (43.2)	136 (84.0)	401 (91.8)	59 (86.8)	1086 (82.1)	1546 (84.6)	1733 (82.2)

^aTDsc: teledermoscopy.

^bFirst GP self-administered question: Would you have referred this patient if TDsc was not available?

^cSecond GP self-administered question: Are you still referring this patient to the dermatologist?

Discussion

Principal Results

This retrospective study assessed the impact of the availability of TDsc on GPs' self-reported decisions to refer patients to the dermatologist. GPs' self-reported initial referral decisions before the TDsc consultation were compared with their referral decisions after the TDsc consultation for skin lesions diagnosed by the TD as (pre)malignant or benign. This study showed that for these lesions, GPs adjusted their initial referral decision after the TD assessment in half of the TDsc consultations.

For 26 (16%) of 162 patients with a premalignant TD diagnosis and for 67 (56.8%) of 118 patients with a malignant TD diagnosis, GPs adjusted their referral decision after the TDsc consultation from nonreferral to referral. Therefore, without the availability of TDsc, GPs would not have referred these patients with (pre)malignant TD diagnoses directly to the dermatologist.

Furthermore, if the TD provided the diagnosis seborrheic keratosis, GPs adjusted their referral decision in 676 (86.2%) of the 784 TDsc consultations from referral to nonreferral. For the TD diagnosis of vascular skin lesions, GPs adjusted their

referral decision in 131 (80.4%) of the 163 TDsc consultations from referral to nonreferral. Therefore, without the availability of TDsc, GPs would have referred these patients with benign skin lesions to a dermatologist.

Comparison With Prior Work

In a Belgian TDsc study, which included all patients with suspicious skin lesions for TDsc, regardless of whether the GPs intended to refer the patients, GPs photographed all skin lesions as part of the TDsc consultation [10]. The vast majority of these skin lesions were assessed by the TD as benign (n=91, 86.7%), malignant (n=8, 7.6%), and uncertain classified diagnoses (n=6, 5.7%). These percentages are comparable with the TD-assessed skin lesions in our TDsc study, in which 81.9% (n=5211) were benign, 8.8% (n=561) were premalignant, and 9.3% (n=592) were malignant.

In contrast to our study, a Danish and a Swedish TDsc study included only patients with suspicious skin lesions that the GPs, without the availability of TDsc, would have referred to the dermatologist [5,6]. All these patients were seen in-person by a dermatologist after the TDsc consultation. These studies reported that 27.7% (n=166) and 28.1% (n=229) of the skin

lesions were diagnosed by the TD as (pre)malignant and 72.3% (n=434) and 71.9% (n=587) were diagnosed as benign, respectively. For the same group of patients in our study, where the GPs indicated that they initially would have referred the patient to the dermatologist, we found a slightly lower percentage of patients with (pre)malignant diagnosed skin lesions (n=873, 20.5%) and a slightly higher percentage of patients with benign diagnosed skin lesions (n=3384, 79.5%).

In these 3 TDsc studies, all patients with suspicious skin lesions, along with patients that the GPs initially would have referred for a physical dermatological consultation, were included. By contrast, in our study, which was performed in daily general practice, GPs acted as gatekeepers to dermatology care. GPs decided themselves whether to apply TDsc, justify a wait-and-see policy, manage the skin condition themselves, or refer the patient to a dermatologist.

Previous findings show that TDsc is especially valuable for the triage of patients with benign skin lesions. The relatively fast TD assessment of skin lesions diagnosed as evidently benign reassures and avoids nervous waiting for both patients and practitioners [15,16]. TDsc also releases the burden on dermatology care since most patients with benign skin lesions can be managed appropriately in GP practice without the need for a physical referral to a dermatologist [5-11]. Moreover, this means that dermatologists can allocate more time to the treatment of patients with complex skin lesions. In addition, patients with severe (pre)malignant skin lesions who need an urgent in-person dermatological evaluation will have improved access to the dermatologist due to the availability of TDsc [5,10,11].

Remarkably, the GPs in our study also applied TDsc to request TD advice concerning nonpigmented benign diagnoses, such as eczema, psoriasis, and insect bites, which is in accordance with 2 other TDsc studies in a virtual lesion clinic and primary health care center setting [9,10]. This implies that GPs also use TDsc as a diagnostic tool to request advice from the TD regarding the management of nonpigmented skin lesions. Dermatologists do not need a dermoscopic photo to assess these types of skin lesions. However, we could not check whether the GPs uploaded a dermoscopic photo for these nonpigmented skin lesions in the TDsc consultation.

The TDsc service evaluated in our study is unique compared to other systems because it asks GPs to enter their initial referral decision at the start of the TDsc consultation request and their final referral decision after the TDsc consultation. In a retrospective TDsc study by our research group 5 years ago in the same nationwide context and with the same Dutch TDsc system, we found that the GPs adjusted their initial referral decision after TDsc in half of the consultations [13]. GPs thus still frequently change their referral decision after a TDsc consultation, which could be because they face difficulties when diagnosing skin lesions or discriminating between benign and malignant skin lesions [1,2,6,17]. GPs might lack this knowledge because dermatology education and skills such as biopsies are underrepresented in the Dutch medical and GP training curriculum [18]. GP residents must obtain this dermatological knowledge from their GP educators during the medicine

internships, and this knowledge transfer might be limited. Furthermore, in the Netherlands, most patients from GP primary care are referred to dermatology secondary care [19]. This again addresses the importance of TDsc as a tool to support GPs in primary practice in recognizing and gaining knowledge on skin lesions and by receiving instructions on patient management. Due to data migration and limitations in the Ksyos database, we could not check if both of our TDsc studies concerned the same GP population. Over the years, some GPs might have learned from the TD advice and applied TDsc less often. It is also possible that GPs who recently started applying the TDsc service frequently change their referral decisions. In any case, the frequently changing referral decisions of GPs emphasize the surplus value and need of TDsc to support GPs in their referral decisions of patients with skin lesions.

In an Italian study, GPs were also asked to assess photographed skin lesions and decide whether they would refer the patient to a dermatologist [3]. The authors of that study did not specify who took the photographs. After a 4-hour training on the classification and management of skin lesions, GPs were again asked about their referral decision for the same set of clinical images of skin lesions. GPs had to base their referral decision solely on the set of submitted clinical images without physically seeing the patients and skin lesions in their GP practice. Furthermore, the GPs did not receive a diagnosis or advice from the TD on which they could base their referral decision. In this Italian study, the number of nonmelanocytic benign skin lesions of patients whom GPs intended to refer to a dermatologist decreased significantly after training on the classification and management of skin lesions. This type of training could consist of e-learning, refreshers, and courses in the GP education programs regarding both taking dermoscopic images and recognizing pigmented skin lesions. Therefore, continuous training of GPs in the Dutch TDsc setting could potentially help reduce the number of referrals of patients with benign skin lesions [1].

Strengths and Limitations

The strengths of this large retrospective study include that TDsc consultations were conducted in daily GP practice and were not simulated in a study setting. The GP referral decisions were noted both before and after the TDsc consultation, which allowed us to verify whether GPs adjusted their initial referral decisions after the TDsc consultation. In doing so, we gained insight into GP referral decisions for different diagnosis groups after the TD assessment in daily GP practice.

On the other hand, the first limitation of our study is that the TDs did not always report their diagnosis in the TDsc system and that we omitted data on the differential diagnosis. This might have resulted in an underestimation of the absolute number of (pre)malignant and benign diagnoses for which TDsc was applied by the GPs. It is possible that TDs were unable to provide a diagnosis because the GPs provided insufficient patient information in the TDsc consultation [20]. Furthermore, overview or dermoscopic photos taken by the GP may have been lacking in the TDsc consultation or may have been of insufficient quality [6,10]. The Ksyos TDsc system does not validate whether a dermoscopic photo of the skin lesion is

available at all and if it is, whether the photo quality is sufficient. GPs can only retake the photos if they receive direct feedback from the TD and if the patient is present at the GP practice. In the future, an algorithm could be created into the TDsc system that assesses the photo quality and provides real-time, direct feedback to the GP if improvements are necessary. Showing instructions in the Ksyos TDsc system (eg, image quality checklist, guidelines on taking dermoscopic photos) could support GPs in filling in the TDsc consultation completely and ensure photos of sufficient quality and correct type (overview, detailed, dermoscopic) [21,22].

The second limitation of our study is that the GPs were not obliged to fill in the self-administered questions regarding their referral decisions; thus, these self-administered questions were not always filled in. For these TDsc consultations, we could not compare the GP referral decision before and after the TDsc consultation. In addition, we do not know if the GP interpreted these questions regarding their referral decision as originally intended in the TDsc system. The reasons why GPs decided not to physically refer patients with a TD-diagnosed (pre)malignant skin lesion are still unknown. Additionally, clinical follow-up data on these patients are lacking. The Dutch guideline for suspicious skin abnormalities recommends that GPs refer malignant skin lesions to the dermatologist [23]. We know from dermatology experience that it is possible for GPs to deviate from this guideline after contact with a dermatologist; for example, for elderly patients, if the GP is experienced in excision of lesions, if the excision has already been performed, or for superficial lesions that do not require invasive treatment. For premalignant diagnoses, TDs also have an important advisory role for GPs on how to treat patients. Referral of premalignant lesions is dependent on the condition (location, involvement, etc). Consultations in which GPs initially did not plan to refer a benign lesion (after confirmation by TDsc) but then changed their decision could be due to an insistent patient. However, we know from dermatology experience that dermatologists have specialized treatment equipment available, such as laser and light therapy. It is also likely that GPs are not aware of these (aesthetic) treatment options before sending the TDsc consultation. The advantage of TDsc is that GPs are

informed about these treatment options due to the TD response and that patients can receive this treatment.

The third limitation is that only the TDsc consultation data extracted from the Ksyos system were accessible for our study. Although Ksyos is the largest store-and-forward telemedicine provider in the Netherlands, the overall number of TDsc consultations in the Netherlands might be higher.

The fourth limitation is that no data concerning the histopathological diagnoses were available for our study. In practice, it is considered unethical to acquire, purely for research purposes, the histopathology of patients with benign skin lesions who not have been referred by the GP to the dermatologist (Q1=No and Q2=No; Q1=Yes and Q2=No). Vestergaard et al [6] showed in a pilot study that patients are reluctant to travel to the dermatologist for assessment of a supposedly benign skin lesion, and GPs are not willing to refer these patients to a dermatologist. Due to the retrospective nature of our study, it was not possible to obtain histopathological data of patients with skin lesions that were referred to dermatology care after the TDsc consultation (Q1=Yes and Q2=Yes; Q1=No and Q2=Yes). We can only presume that GPs would have immediately referred patients to the dermatologist if patients had skin lesions that were highly suspect of melanoma or dubious.

Conclusions

This study showed that GPs adjusted their initial referral decision of patients with skin lesions in half of the studied TDsc consultations after the TD assessment. The availability of TDsc remains thus of added value to support GPs in gatekeeper health care systems in their decision to refer patients to a dermatologist for an in-person consultation. This study has shown that GPs initially did not intend to refer patients with (pre)malignant skin lesions for an in-person dermatological consultation and that the availability of TDsc aids in the referral of these patients. In addition, TDsc supports GPs in the prevention of unnecessary physical referrals to the dermatologist for patients with low complex benign skin lesions (eg, seborrheic keratosis and vascular skin lesions), easing the burden on dermatology care.

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Authors' Contributions

ET, FvS, MWB, and LWP conceptualized the study. All authors were involved in the study design. ET and FvS were responsible for data acquisition. All authors were involved in the analysis and interpretation of data. ET, FvS, and LWP wrote the manuscript from the first version onward. MWB and MWJ were further involved in critical revision of the manuscript.

Conflicts of Interest

ET and FvS are PhD researchers at the Amsterdam University Medical Center (UMC) and employed by Ksyos.

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Abbreviations

GP: general practitioner

ICD-10: International Classification of Diseases, 10th revision

TD: teledermatologist

TDsc: teledermoscopy

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Research Letter

A Gender Lens on User Quality Ratings From Young Teenagers Assessing the Sun Safe App: Comparing Responses From Co-researchers and Participants of Pilot Intervention Studies

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KEYWORDS

app development; co-design; sun exposure; sun protection; teenager; uMARS; UV index; vitamin D; young adolescents; sunburn; adolescent; smartphone; gender; sun; protection; app; engagement; sunburn; risk; melanoma; decision-making

Introduction

We developed the iOS smartphone app *Sun Safe* to support healthy sun practices in young teenagers (aged 12-13 years) [1]. The production involved co-design with young *co-researchers* (ie, aged 12-13 years) with a health message of using sun protection when the UV index is ≥ 3 [1]. Important features include real-time and location-specific weather data on the UV index and gamified educational content [1,2].

We were concerned that indifferent attitudes expressed by male co-researchers during the development of *Sun Safe* [3] would translate into gendered differences in user quality ratings. Furthermore, we wondered whether involvement in the co-design process could bias quality assessments. The results presented in this letter compare the responses of co-researchers [1] with those of participants of the pilot intervention studies [4].

Methods

All methods underpinning the development of the app and pilot intervention studies are described elsewhere [1,4]. Data were collected from co-researchers (n=15, 9 female and 6 male co-researchers) involved in the co-design of *Sun Safe* across a 10-month period (2018-2019) via telephone interviews or 2-hour in-person workshops (3 were run) [1]. Data were collected from participants (n=24, 17 female and 7 male participants) of

placebo-controlled pilot intervention studies, which tested *Sun Safe* for 6 weeks (2020) [4]. Co-researchers downloaded and used the beta version of *Sun Safe* (via *TestFlight*) for 20 minutes during the final workshop (June 18, 2019) [1]. Pilot study participants accessed the fully developed app (v1.0.1, 2020) for 6 weeks in 2020 [4]; they also identified their gender (male, female, other, prefer not to say), age, and postcode of residence during recruitment. User quality ratings data were collected using the User Version of the Mobile Application Rating Scale (uMARS) [4].

Results

There were twice as many recruited female participants (n=26) as male participants (n=13). Co-researchers were older (mean 13.8, SD 0.4 years) than pilot study participants (mean 12.7, SD 0.4 years). Most co-researchers used the app for 5-10 minutes (8/15, 53%); most pilot study participants used it every day or on most days (13/24, 55%).

Female co-researchers responded to more questions than male co-researchers (Table 1). Within *subjective quality* and *perceived impact*, male pilot study participants rated the *Sun Safe* app higher for *overall star rating* and *help-seeking* behaviors (Table 1).

Female pilot participants scored *Sun Safe* lower for *engagement* than female co-researchers (Figure 1).

Table 1. User quality ratings (User Version of the Mobile Application Rating Scale survey results) of the Sun Safe app for the subjective quality and perceived impact areas of assessment.

	Co-researchers			Pilot study participants		
	Male ^a	Female	<i>P</i> value	Male	Female	<i>P</i> value
Participants, n	6	9	N/A ^b	7	17	N/A
Questions completed ^{c,d} , n/N (%)	89/156 (57.1)	226/234 (96.6)	N/A	181/182 (99.5)	442/442 (100.0)	N/A
Subjective quality^{e,f}						
Recommended ^g , mean (SD)	3.3 (2.1)	3.6 (0.5)	.63	3.7 (1.1)	3.1 (1.1)	.26
App use ^h , mean (SD)	3.0 (1.7)	4.1 (0.8)	.24	3.9 (0.7)	3.3 (1.2)	.37
Pay for app?ⁱ, n						
Yes	0	3	N/A	0	3	N/A
No	3	6	N/A	7	14	N/A
Overall star rating ^j , mean (SD)	4.2 (0.5)	3.6 (0.8)	.15	4.7 (0.7)	3.2 (0.9)	<.001
Perceived impact^{e,k}, mean (SD)						
Awareness ^l	3.7 (0.6)	3.7 (0.8)	>.99	4.0 (0.5)	3.4 (1.1)	.17
Knowledge ^m	4.0 (0.0)	4.0 (0.7)	>.99	3.9 (0.7)	3.4 (1.2)	.54
Attitudes ⁿ	3.0 (0.0)	3.4 (1.1)	.75	3.6 (0.8)	3.4 (0.9)	.79
Intention to change ^o	3.3 (0.6)	3.9 (0.8)	.41	4.1 (0.9)	3.4 (1.1)	.17
Help-seeking ^p	3.7 (1.2)	3.7 (0.7)	>.99	3.9 (1.1)	2.7 (1.0)	.04
Behavior change ^q	4.0 (1.0)	3.7 (1.0)	.75	4.0 (0.8)	3.1 (1.1)	.09

^aTwo male participants did not complete any questions.

^bN/A: not applicable.

^cTotal number of questions completed; 26 questions could be completed within the User Version of the Mobile Application Rating Scale (uMARS) survey by each participant.

^dPercentage of questions completed of total possible (= total number completed by all participants / (n × 26) × 100), with statistical comparisons of the total number of uMARS survey questions completed (of 26), using Fisher Exact test, between male and female co-researchers (relative risk [RR] 0.60, 95% CI 0.50-0.70; *P*<.001) and pilot study participants (RR 0.99, 95% CI 0.97-1.00; *P*=.29).

^eThe *P* values are the results of Mann-Whitney tests comparing data by gender (except for *Pay for app?*).

^fAcross 4 questions, participants rated the subjective quality of the app, using 5-point scales (see below) or yes/no for *Pay for app?*

^gWould you recommend this app to people who might benefit from it? (from 1, not at all, to 5, definitely).

^hHow many times do you think you would use this app in the next 12 months? (from 1, none, to 5, >50 times).

ⁱWould you pay for this app? Yes is the number of participants answering *yes*; no is the number of participants answering *no*.

^jWhat is your overall star rating of the app? (from * to *****; *One of the worst apps I've used* to *One of the best apps I've used*).

^kAcross 6 questions, participants rated the app based upon perceived capacity to modify awareness, knowledge, attitudes, intention to change, likelihood to seek help, and behaviors related to their sun health, using a 5-point scale of *strongly disagree* (1) to *strongly agree* (5).

^lThis app has increased my awareness of the importance of addressing sun health behaviors.

^mThis app has increased/changed my knowledge of sun health behaviors.

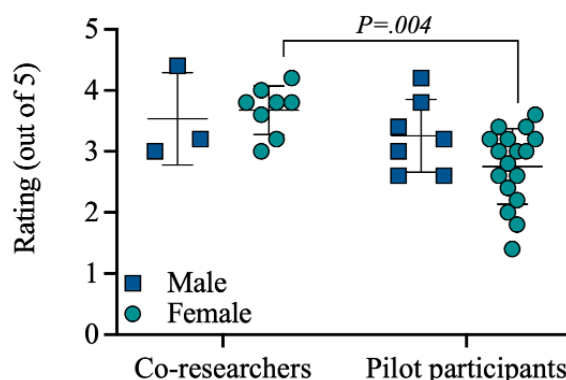
ⁿThis app has changed my attitudes toward improving my sun health behaviors.

^oThis app has increased my intentions/motivation to address my sun health behaviors.

^pThis app would encourage me to seek further help to address my sun health behaviors (if needed).

^qUse of this app will change my sun health behaviors.

Figure 1. Female pilot study participants rated Sun Safe lower in the engagement area of assessment. Mean scores for questions asked across the engagement area of assessment are shown individually for each co-researcher (3 male and 8 female) and pilot study (7 male and 17 female) participant. Data are shown as mean (SD). Two-way ANOVA was used to compare differences (participant type x gender), with Tukey post hoc tests identifying a statistically significant difference in predicted means of 0.92 (95% CI 0.24-1.60; $P=.004$) between female co-researchers and female pilot study participants. The five questions were posed, and 5-point Likert scales within this area of assessment were as previously published.



Discussion

Overall, few differences in app quality ratings were observed by gender, suggesting that *Sun Safe* was equally acceptable for use by young men and women even though fewer male participants were recruited to develop and test *Sun Safe* [1].

Pilot study participants rated *Sun Safe* lower for *engagement*, highlighting the importance of an independent review. Limitations included the relatively small sample size, differences in review time, and ongoing challenges in defining the influences of biological sex and gender on health outcomes [5]. Additional consumer engagement will help determine how games and gamification could be further built into *Sun Safe*.

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Conflicts of Interest

None declared.

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Short Paper

Photosensitivity From Avapritinib: Pharmacovigilance Analysis

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Abstract

Certain protein kinase inhibitors have been reported to cause photosensitivity. Avapritinib is a tyrosine kinase inhibitor that was approved in January 2020. The aim of this analysis was to determine if a statistically significant signal exists between Avapritinib and photosensitivity in the real-world population. A disproportionality analysis was conducted using the Food and Drug Administration Adverse Event Reporting System (FAERS) from January 1, 2020, to December 31, 2021. A literature review was also performed to identify case reports of Avapritinib-induced photosensitivity. A total of 13 adverse event reports with Avapritinib as the drug and photosensitivity as the reaction were identified in FAERS. Avapritinib was the suspect drug in all 13 reports, and in 12 of the 13 reports, Avapritinib was the only drug listed. Disproportionality analysis found a proportional reporting ratio of 11.0, $\chi^2_1=107$, reporting odds ratio of 11.0, and a lower limit of the 95% CI of the information component of 2.1. The literature review found 1 case report of Avapritinib-induced photosensitivity in a patient who had been taking Avapritinib 300 mg daily for 5 months. A statistically significant signal was found between Avapritinib use and photosensitivity. Clinicians should continue to balance the benefits and risks when prescribing Avapritinib to patients.

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oncology; Avapritinib; drug-induced; adverse reaction; photosensitizer; photosensitizing; cancer; pharmacovigilance; pharmaceutical; photosensitive; photosensitivity; light; adverse event; side effect; tumor; pharmacology

Introduction

Humans have been exposed to UV light for millions of years. This exposure has beneficial effects in increasing vitamin D levels and in treating psoriasis, vitiligo, atopic dermatitis, and scleroderma among others [1]. However, this same UV light can increase the risk of skin carcinoma, cataracts, and age-related macular degeneration. Certain drugs have been found to increase the sensitivity of the skin to sunlight. These drugs are categorized as sun-sensitizing drugs and can lead to drug-induced photosensitivity. Drug-induced photosensitivity can present as erythema and can progress to blisters, bullae, and severe pain. Knowing which drugs can lead to drug-induced photosensitivity is paramount so that clinicians can adequately advise patients on sun protection and reduce the risk of skin cancer.

Certain protein kinase inhibitors such as Vemurafenib, Vandetanib, and Imatinib have been reported to cause photosensitivity [2,3]. Avapritinib is a tyrosine kinase inhibitor that was approved in January 2020 and is used for the treatment of systemic mastocytosis and unresectable or metastatic gastrointestinal stromal tumor. Because Avapritinib has been in the market for such a short period of time, adverse reactions attributed to the drug are still being discovered. In 2021, the Food and Drug Administration (FDA) issued an alert that they are evaluating the need for regulatory action on the potential signal of photosensitivity from Avapritinib [4]. The objective of this analysis was to determine if a statistically significant signal exists between Avapritinib and photosensitivity in the real-world population.

Methods

Adverse event reports from the FDA Adverse Event Reporting System (FAERS) [5] from January 1, 2020, to December 31, 2021, were downloaded. Reports were filtered to those with the drug Avapritinib and the MedDRA [6] term photosensitivity reaction. Reports were further filtered to those with Avapritinib as the suspect drug, and duplicate cases were removed. Disproportionality analysis was performed to identify if a significant signal exists between the drug and adverse event of interest. Statistical analysis was carried out in SAS [7] version 9 (SAS Institute). A literature review using PubMed [8] was performed to identify case reports of Avapritinib-induced photosensitivity.

Results

A total of 13 adverse event reports with Avapritinib as the drug and photosensitivity as the reaction were identified in FAERS with the earliest report in May 2020 and the latest in November 2021. The most common coreported events were edema, increased lacrimation, fatigue, rash, abdominal discomfort, and diarrhea. Avapritinib was the suspect drug in all 13 reports, and in 12 of the 13 patients, Avapritinib was the only drug listed. In the other case report, the patient was taking insulin glargine,

insulin aspart, ondansetron, diphenhydramine, loratadine, loperamide, bisacodyl, and tramadol in addition to Avapritinib. All 13 reports originated from the United States. In addition, in 5 cases, the adverse event resulted in death, a life-threatening condition, hospitalization, disability, congenital anomaly, or other serious condition. However, the case reports do not specify the cause of the above serious conditions. It may be related to photosensitivity, the underlying condition for which the patient was being treated, or another unknown cause. The average age of the patients was 60 years with a range of 31 to 80 years. A total of 11 patients were men, and the remaining 2 were women. The indication for the use of Avapritinib was gastrointestinal stromal tumor in 9 of the patients and systemic mastocytosis in the remaining 5 (Table 1). Disproportionality analysis found a proportional reporting ratio (PRR) of 11.0, $\chi^2=107$, reporting odds ratio (ROR) of 11.0, and the lower limit of a 95% CI of the information component (IC_{025}) of 2.1.

The signal between Avapritinib and photosensitivity was statistically significant based on each of the following three criteria:

1. PRR \geq 2, chi-square \geq 4, and number of events \geq 3 [9]
2. ROR $>$ 1 [10]
3. $IC_{025}>$ 0 [11]

Table 1. Demographic data of patients with Avapritinib use and photosensitivity reaction.

	Cases of Avapritinib and photosensitivity reaction (N=13), n (%)
Gender	
Male	11 (85)
Female	2 (15)
Age (years)	
31-50	3 (23)
51-60	2 (15)
61-70	5 (38)
71-80	2 (15)
Unknown	1 (8)
Indication for use of Avapritinib	
Gastrointestinal stromal tumor	9 (69)
Systemic mastocytosis	4 (31)
Seriousness	
Resulted in death, a life-threatening condition, hospitalization, disability, congenital anomaly, or other serious condition	5 (38)
Did not result in above	8 (62)

Discussion

The literature review found 1 case report of Avapritinib-induced photosensitivity [12]. This patient was a 56-year-old female who was being treated for a stage IV gastrointestinal stromal tumor with Avapritinib. She presented with a rash that initially appeared as a sunburn and progressed to the development of bullae and pain. Histopathology identified dermal edema, mixed

inflammatory infiltrates, rare dyskeratotic keratinocytes, and follicular interface. The patient had been on Avapritinib 300 mg daily for 5 months when the rash first occurred. The patient was diagnosed with Avapritinib-induced photosensitivity. Avapritinib was permanently discontinued, and 0.1% triamcinolone cream was initiated with improvement in the rash. Further, nonclinical findings of phototoxicity with Avapritinib use were found in vitro mouse fibroblasts and in vivo rat studies [13]. The European Medicines Agency lists a warning of

photosensitivity with Avapritinib and a 1.1% incidence of photosensitivity during clinical trials [14].

The pathophysiology behind the photosensitivity from Avapritinib has not been fully elucidated but may share a similar mechanism to the cutaneous toxicities of other tyrosine kinase inhibitors such as imatinib. For example, Imatinib inhibits activity of the c-KIT gene leading to hypopigmentation and reduced protection against UV exposure [2]. Similarly, Avapritinib is also a potent inhibitor of the KIT gene [15]. Further studies are needed to identify the pathophysiology underlying this possible reaction.

FAERS provides a passive pharmacovigilance risk signal and does not by itself demonstrate causal associations. The adverse event may be a result of the drug, the underlying disease, or a combination of the two. Individual case causality assessments, periodic aggregate assessment of available clinical safety data, and well-designed randomized controlled clinical trials are needed to validate the safety signal and to assess for an

association between an adverse event and a drug [16]. In addition, not every adverse event is reported to the FDA and thus incidence of the adverse event cannot be calculated. Further, the time to onset of the adverse event from initiation of the drug is not provided in FAERS. If there is a long latency period to the development of the adverse event, the benefit of the drug may be more likely to supersede the risk. However, FAERS has advantages in identifying signals in a large and diverse patient group in the real world that are not always identified in the early clinical trials [17,18].

A statistically significant signal was found between Avapritinib use and photosensitivity. Of these adverse event reports of Avapritinib and photosensitivity, 85% (n=11) of the reports were in male patients and 15% (n=2) in female patients. Further studies are needed to evaluate whether the disproportionality signal between Avapritinib and photosensitivity represents a causal association. Clinicians should continue to balance the benefits and risks when prescribing Avapritinib to patients.

Conflicts of Interest

None declared.

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Abbreviations

FAERS: Food and Drug Administration Adverse Event Reporting System

FDA: Food and Drug Administration

IC₀₂₅: lower limit of a 95% CI of the information component

PRR: proportional reporting ratio

ROR: reporting odds ratio

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Short Paper

An Evaluation of Primary Studies Published in Predatory Journals Included in Systematic Reviews From High-Impact Dermatology Journals: Cross-sectional Study

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Abstract

Background: Predatory publishing is a deceptive form of publishing that uses unethical business practices, minimal to no peer review processes, or limited editorial oversight to publish articles. It may be problematic to our highest standard of scientific evidence—systematic reviews—through the inclusion of poor-quality and unusable data, which could mislead results, challenge outcomes, and undermine confidence. Thus, there is a growing concern surrounding the effects predatory publishing may have on scientific research and clinical decision-making.

Objective: The objective of this study was to evaluate whether systematic reviews published in top dermatology journals contain primary studies published in suspected predatory journals (SPJs).

Methods: We searched PubMed for systematic reviews published in the top five dermatology journals (determined by 5-year h-indices) between January 1, 2019, and May 24, 2021. Primary studies were extracted from each systematic review, and the publishing journal of these primary studies was cross-referenced using Beall's List and the Directory of Open Access Journals. Screening and data extraction were performed in a masked, duplicate fashion. We performed chi-square tests to determine possible associations between a systematic review's inclusion of a primary study published in a SPJ and particular study characteristics.

Results: Our randomized sample included 100 systematic reviews, of which 31 (31%) were found to contain a primary study published in a SPJ. Of the top five dermatology journals, the *Journal of the American Academy of Dermatology* had the most systematic reviews containing a primary study published in an SPJ. Systematic reviews containing a meta-analysis or registered protocol were significantly less likely to contain a primary study published in a SPJ. No statistically significant associations were found between other study characteristics.

Conclusions: Studies published in SPJs are commonly included as primary studies in systematic reviews published in high-impact dermatology journals. Future research is needed to investigate the effects of including suspected predatory publications in scientific research.

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KEYWORDS

predatory journals; systematic review; general dermatology; dermatology; publishing; publications; journals; scientific communication; data; quality; meta-analysis; peer review; primary studies; research; evidence synthesis; articles

Introduction

Predatory publishing is described as a “nebulous concept of research journal publishers who use unethical business practices, minimal or no peer review, or limited editorial oversight to publish articles that are below a minimally accepted standard of quality” [1]. Increasing rates of predatory publishing are accompanied by an equally growing concern surrounding their threat to evidence synthesis and decision-making [1,2]. Predatory publishing can be problematic to our highest standard of scientific evidence—systematic reviews (SRs)—through the inclusion of poor-quality and unusable data, which could mislead results, challenge outcomes, and undermine confidence due to suspected predatory journals (SPJs) having a less rigorous peer review process.[3] Evidence is lacking as to whether studies published in SPJs are frequently included as primary studies in SRs; therefore, we aimed to evaluate whether SRs published in top dermatology journals contain primary studies published in SPJ.

Methods

We searched PubMed (using the Advanced Search filters) for SRs published in the top five dermatology journals (determined by 5-year h-indices) between January 01, 2019, and May 24, 2021. The returned SRs (N=339) were downloaded as a comma-separated values file. We randomized the returns and selected the first 100 articles to examine. Primary studies were extracted from each systematic review, and the publishing journal of these primary studies was cross-referenced using Beall’s List (archived and updated versions [4]) and the Directory of Open Access Journals (DOAJ) [5], both widely used and publicly available databases of suspected predatory or questionable journals. To determine if certain study characteristics were associated with the inclusion of SPJs, the

following characteristics were extracted: (1) whether the SR received funding; (2) whether the SR had a registered protocol; (3) whether the SR included randomized controlled trials, nonrandomized studies of interventions, or both as primary studies; (4) the year the SR was published; and (5) the databases the SR searched for primary studies, to determine if certain study characteristics were associated with the inclusion of SPJs. Screening and data extraction were performed in a masked, duplicate fashion by authors BH and KS, in accordance with best practices [6]. We performed chi-square tests to determine possible associations between an SR’s inclusion of a primary study published in an SPJ and particular study characteristics.

This study did not use human subjects and thus did not require institutional review board oversight.

Results

Our randomized sample included 100 SRs, of which 31 (31%) SRs were found to contain a primary study published in an SPJ. A total of 53 primary studies were published across 22 unique SPJs. Of the top five dermatology journals, the *Journal of the American Academy of Dermatology* had the most SRs containing a primary study published in an SPJ (Table 1). The majority of suspected predatory publications (28/55, 51%) were published in the *Indian Journal of Dermatology*, *Venereology*, and *Leprosy*. SRs that contained a meta-analysis were significantly less likely to contain a primary study published in an SPJ ($P=.002$; Table 1). Additionally, SRs that had a registered protocol were less likely to contain a primary study published in an SPJ ($P=.02$). No statistically significant associations were found between journals, year of publication, included primary study types (eg, randomized controlled trials, nonrandomized studies of interventions, or both), funding, or databases included in the SR search.

Table 1. Characteristics of systematic reviews with and without primary studies published in predatory journals (N=100).

Study characteristics	Contains a primary study published in a suspected predatory journal, n (%)			Chi-square (<i>df</i>)	P value
	No	Yes	Total		
Journal				3.69 (4,1)	.45
<i>Journal of the American Academy of Dermatology</i>	26 (26)	17 (17)	43 (43)		
<i>British Journal of Dermatology</i>	12 (12)	4 (4)	16 (16)		
<i>Journal of Investigative Dermatology</i>	1 (1)	0 (0)	1 (1)		
<i>Journal of the European Academy of Dermatology and Venereology</i>	19 (19)	8 (8)	27 (27)		
<i>Jama Dermatology</i>	11 (11)	2 (2)	13 (13)		
Year of publication				0.64 (2,1)	.07
2019	24 (24)	13 (13)	37 (37)		
2020	30 (30)	11 (11)	41 (41)		
2021	15 (15)	7 (7)	22 (22)		
Systematic review contained a meta-analysis				9.38 (1,1)	.002
No	20 (20)	19 (19)	39 (39)		
Yes	49 (49)	12 (12)	61 (61)		
Study received funding				2.69 (1,1)	.10
No	47 (47)	26 (26)	73 (73)		
Yes	22 (22)	5 (5)	27 (27)		
Includes search from PubMed				0.06 (1,1)	.81
No	36 (36)	17 (17)	53 (53)		
Yes	33 (33)	14 (14)	47 (47)		
Includes search from Web of Science				0.39 (1,1)	.53
No	53 (53)	22 (22)	75 (75)		
Yes	16 (16)	9 (9)	25 (25)		
Includes search from Cochrane				0.15 (1,1)	.70
No	35 (35)	17 (17)	52 (52)		
Yes	34 (34)	14 (14)	48 (48)		
Includes search from Trial Registries				0.90 (1,1)	.34
No	47 (47)	24 (24)	71 (71)		
Yes	22 (22)	7 (7)	29 (29)		
Includes search from Embase				3.77 (1,1)	.05
No	14 (14)	12 (12)	26 (26)		
Yes	55 (55)	19 (19)	74 (74)		
Systematic reviews of RCTs^a, NRSIs^b, or both				1.66 (2,1)	.44
RCTs only	12 (12)	4 (4)	16 (16)		
NRSIs only	37 (37)	14 (14)	51 (51)		
Both RCTs and NRSIs	20 (20)	13 (13)	33 (33)		
Systematic review had a protocol				5.78 (1,1)	.02
No	41 (41)	26 (26)	67 (67)		
Yes	28 (28)	5 (5)	33 (33)		

^aRCT: randomized controlled trial.

^bNRSI: nonrandomized studies of interventions.

Discussion

We found that studies published in SPJs are commonly included as primary studies in SRs published in high-impact dermatology journals. SRs that contained a meta-analysis were less likely to have a primary study published in an SPJ, which is a promising finding, as research has shown that studies published in predatory journals are of lower quality [1,3]. Interestingly, SRs that registered a protocol were significantly less likely to include a primary study published in an SPJ. We suspect this finding may be because authors of SRs with registered protocols may have more diligence and time to confirm that sources of publications were not published in an SPJ. In our sample, the majority of primary studies from SPJs were published in the *Indian Journal of Dermatology, Venereology, and Leprology*—which was removed from the DOAJ directory secondary to the journal failing to adhere to best practice [5]. Although considered to be an SPJ, this journal's articles are included in Embase and PubMed searches. Interestingly, 83% (44/53) of the studies published in SPJs were PubMed indexed.

One way through which studies published in SPJs can obtain PubMed indexing is “backdoor publishing” via PubMed Central or the National Center for Biotechnology Information Bookshelf [7]. Currently, there is little direction on how to best manage SPJs; however, the consensus is that studies published in SPJs should be omitted because of their potential impact on data synthesis. Due to their potential threat to SRs and scientific evidence, we recommend that authors of SRs verify their primary studies by using Beall's List and the DOAJ directory—a recommendation proposed by other studies exploring ways to minimize the inclusion of studies published in SPJs in SRs [8,9].

Our study's limitations include only searching SRs using PubMed and only using Beall's List and DOAJ lists of questionable journals. Additionally, authors of SRs included in this study may have unknowingly included an SPJ, as some SPJs were added to Beall's List and the DOAJ lists of questionable journals after the SR was already published, which is another limitation of our study. Lastly, future research is needed to investigate the effects of including SPJ publications in scientific research.

Conflicts of Interest

MV reports research grants from the NIH, the Office of Research Integrity, and the Oklahoma Center for the Advancement of Science and Technology (OCAST) unrelated to this work.

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Abbreviations

DOAJ: Directory of Open Access Journals
SPJ: suspected predatory journal
SR: systematic review

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Original Paper

Development of a Website for a Living Network Meta-analysis of Atopic Dermatitis Treatments Using a User-Centered Design: Multimethod Study

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Abstract

Background: A rapid expansion of systemic immunological treatment options for atopic dermatitis (AD) has created a need for clinically relevant and understandable comparative efficacy and safety information for patients and clinicians. Given the scarcity of head-to-head trials, network meta-analysis (NMA) is an alternative way to enable robust comparisons among treatment options; however, NMA results are often complex and difficult to directly implement in shared decision-making.

Objective: The aim of this study is to develop a website that effectively presents the results of a living systematic review and NMA on AD treatments to patient and clinician users.

Methods: We conducted a multimethod study using iterative feedback from adults with AD, adult caregivers of children with AD, dermatologists, and allergists within a user-centered design framework. We used questionnaires followed by workshops among patients and clinicians to develop and improve the website interface. Usability testing was done with a caregiver of a patient with eczema.

Results: Questionnaires were completed by 31 adults with AD or caregivers and 94 clinicians. Patients and caregivers felt it was very important to know about new treatments (20/31, 65%). Clinicians felt the lack of evidence-based comparisons between treatments was a barrier to care (55/93, 59%). "Avoiding dangerous side effects" was ranked as the most important priority for patients (weighted ranking 5.2/7, with higher ranking being more important), and "improving patients' overall symptoms" was the most important priority for clinicians (weighted ranking 5.0/6). A total of 4 patients and 7 clinicians participated in workshops; they appreciated visualizations of the NMA results and found the website valuable for comparing different treatments. The patients

suggested changes to simplify the interface and clarify terminology related to comparative efficacy. The user in the usability testing found the website intuitive to navigate.

Conclusions: We developed a website, “eczematherapies.com,” with a user-centered design approach. Visualizations of NMA results enable users to compare treatments as part of their shared decision-making process.

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KEYWORDS

atopic dermatitis; skin; dermatology; dermatitis; eczema; network meta-analysis; knowledge translation; health literacy; user-centered design; patient education; information seeking; health information; website development; web development; web design; website design; allergist; user experience; interface; usability; visualization; decision-making; online resource; education material

Introduction

Progress in understanding the immunopathogenesis of atopic dermatitis (AD) has resulted in an expansion of systemic immunomodulatory treatments. A recent review found over 70 compounds being studied in clinical trials [1]. Expanded therapeutic options should improve outcomes for people with AD, but treatment decisions may become more complex. Comparing the relative effectiveness and safety of different medications is challenging because most clinical trials are placebo-controlled, with few head-to-head trials [2,3]. Network meta-analysis (NMA) can address this gap by using direct and indirect evidence to compare treatments with each other, including treatments that have never been compared with each other in a head-to-head trial [2,4]. We conduct a *living* systematic review and NMA of systemic immunomodulatory treatments for AD that is updated regularly to provide up-to-date comparative evidence [2,3].

Living NMAs have great potential to facilitate continuous knowledge synthesis across different fields of medicine, but the outputs of NMAs can be challenging to interpret for patients and clinician end users. There are resources on creating NMA network diagrams and forest plots for publication [4,5], but these are often complex and may not be clinically meaningful. Some groups have attempted to share NMA results using an open science approach by making their living NMAs available on websites [6-9], but these websites resemble traditional knowledge translation outputs such as journal publications and conference presentations; understanding the results is likely difficult for non-researcher knowledge users [10]. Clinicians and patients without training in interpreting NMA results would not likely be able to use this information directly for treatment decisions. Stakeholder engagement in the website design process could improve uptake and dissemination of NMA results [11].

Our overall goal is to provide reliable information on the relative efficacy and safety of systemic treatments for AD and to help inform clinical shared decision-making. The objective of this study was to develop a website to effectively present the results of our living systematic review and NMA of AD treatments to patients and clinicians.

Methods

Study Design and Setting

To design and develop the website, we used a multimethod user-centered approach. User-centered design has been shown to increase the overall adoption and impact of health tools [12]. We used best practices for user-centered design of decision aids, including a 3-phased iterative approach, with feedback from patients and clinicians [13]. Our team consisted of clinicians, a patient partner, digital product designers, and web developers. The development process took place between September 2019 and April 2020 in Toronto, Ontario, Canada. We completed the study in the following three phases: (1) patients and caregivers of patients with AD and clinicians who treat AD completed questionnaires about meaningful criteria for seeking evidence-based information regarding AD treatments; (2) two workshops, one with patients and caregivers and another with clinicians, assessed how participants perceived and wanted to see the NMA results on the web interface; and (3) usability testing with a caregiver was conducted to identify the remaining barriers and receive feedback about navigation and usability of the website.

Ethics Approval

This study was approved by the Women’s College Hospital Research Ethics Board (REB# 2019-0095-E).

Website Design

Two digital product designers worked with the study investigators to design a prototype with visualizations of the NMA results. We chose to use horizontal bar charts to display the effectiveness of each of the treatments within a specific priority type. The bars represent surface under the cumulative ranking curve (SUCRA) values, an NMA output used to rank treatments within a given outcome; higher values, to a maximum of 100%, indicate better efficacy [4]. The decision to use this type of graphic was made as it is a visualization understood by a wide audience and allows for a simple way of comparing complex data, where concrete numbers and percentages may have misrepresented the results of the NMA.

The different colors within the priority groups allow users to easily scan the page for that individual priority, and the white splitters within the bars act as visual markers to help users see how much of the bar is filled, without calling out a specific

SUCRA percentage (because precise SUCRA point estimates oversimplify results).

The color fills on the bar charts are based on the data collected in the NMA, and therefore the lengths of the bars will only change when new data are analyzed and incorporated into the tool. The interactive component of this website comes into play when comparing one drug to another. Based on their first assessment of the represented graphics, users can select 2 medications they would like to compare side by side; they can view a table that, using written word and a large green checkmark, will clearly identify which of the 2 drugs is currently the most effective treatment option for a given priority, and help them decide which treatment may be better suited for them.

Phase 1

Adults with AD and caregivers of children with AD were recruited from dermatology clinics at Women's College Hospital. To be included, participants had to be 18 years or older and speak English. Consenting participants were given paper questionnaires to complete during clinic visits ([Multimedia Appendix 1](#)). At the end of the questionnaire, participants could opt in or out of being contacted about participating in the workshops.

A web-based questionnaire was circulated to allergists and dermatologists through the Canadian Dermatology Association and the Canadian Society of Allergy and Clinical Immunology mailing lists ([Multimedia Appendix 1](#)). Participation was anonymous.

Phase 2

Workshops took place at Women's College Hospital. Adults with AD and caregivers who indicated their interest in workshops on the Phase 1 questionnaires were recruited. Convenience sampling was used to recruit participants for the clinician workshop; email invitations were sent to dermatologists in the Toronto area.

Participants were shown a prototype of the website on a large television screen. Digital product designers navigated through various sections of the website to focus the discussion on the content, layout or hierarchy of information, and visualization of NMA results. Because of the different levels of familiarity with medical terminology between patients and clinicians, we decided to develop 2 separate web pages to tailor to each user group's needs. The patient group shared their user experience and commented on the language on the home page, patient landing page, and 2 versions of the patient NMA results page. The clinician group was guided through the home page, clinician landing page, and research page. They shared their comments on the language and their expectations for each subsection.

The workshops were audio recorded. Two digital product designers took notes during the workshops and grouped the comments into high, medium, and low priority. High-priority

items were those that were agreed upon by several participants and were perceived as valuable for improving website usability. Low-priority items were expressed by 1 or 2 participants and did not significantly affect how they used the website.

The designers and clinician researchers reviewed the suggestions and decided which priorities were critical or feasible to implement on a new version of the website.

Phase 3

A caregiver of a patient with AD completed usability testing of the updated website, facilitated by 2 designers and 1 clinician (AMD). They reviewed the home page, "About Us" page, patient page (both results for children and for adults), and the experimental drugs page. The digital designers took notes and sorted the comments into high, medium, and low priority using the same criteria as the workshops. Additional information and revision of language were added to the final version of the website.

Statistical Analysis

Descriptive statistics were used to summarize the questionnaire data. For ranking questions, the average ranking was calculated for each answer choice. Weights were applied in reverse; with the most preferred choice (ranked first) given the highest weight and the least preferred choice (ranked last) given the weight of 1. The answer choice with the highest average ranking is the most preferred choice.

Results

Patient Questionnaire Results

Questionnaires were completed by 31 adults with AD or caregivers ([Table 1](#)). Of these, 22 (71%) participants indicated they or their child have been on or have considered using systemic medications. Most participants (20/31, 65%) felt it was very important to know about new treatment options with a 10/10 rating. Most participants learned about new treatments from their doctor (29/31, 98%).

Participants felt effectiveness and side effects were very important information when learning about a new treatment. Other considerations when deciding on a new treatment include cost or insurance coverage, convenience, and length of treatment. "Avoiding potentially dangerous side effects" (5.2/7 weighted ranking; higher ranking indicates higher importance) and "improvement in quality of life" (4.9/7) were ranked the most important considerations.

When asked what they would do next with information about a new treatment option that aligns with their needs, most participants responded they would speak with their doctor. Most participants (16/31, 52%) were interested in knowing about drugs that are only available in countries outside of Canada.

Table 1. Demographics of patient questionnaire respondents (n=31).

Characteristics	Values, n (%)
Age range	
18-39	22 (71)
>40	9 (29)
Sex	
Female	18 (58)
Male	13 (42)

Clinician Questionnaire Results

Clinician questionnaires were completed by 94 participants (Table 2). Most (85/94, 90%) clinicians were seeing patients with AD at their practice. Many clinicians (55/93, 59%) felt the lack of evidence-based comparisons between treatment options was a barrier to patient care.

Clinicians ranked improvement in patients' symptoms (5.0/6 weighted ranking; higher ranking indicated higher importance) and quality of life (4.0/6) as the highest priorities when deciding on a treatment. Other considerations when treating AD include

age of patient, patient preference, and ease of use. They believed that efficacy, safety, and cost were the most important factors for their patients.

Most clinicians (60/90, 67%) indicated they would tell their patients about treatments that are not yet approved with the purpose of potentially enrolling patients into available trials or to give them hope. When asked where they are currently accessing research about treatment options, most clinicians mentioned journal articles and academic meetings as their primary sources of information.

Table 2. Demographics of clinician questionnaire respondents (n=94).

Characteristics	Values, n (%)
Age range	
18-39	42 (45)
40-59	31 (33)
>60	21 (22)
Sex^a	
Female	55 (59)
Male	38 (40)
Number of years in practice	
Still in residency	7 (8)
Less than 5 years	28 (30)
6-10 years	11 (12)
11-20 years	20 (22)
21-30 years	8 (9)
>30 years	19 (20)
Type of practice	
Community	44 (47)
Academic	17 (18)
Community and academic	33 (35)

^aParticipants can choose not to say as a response to this question.

Patient Workshop Results

A total of 4 participants (mean age 39 [SD 21.28] years; 2/4, 50% female; mean age at AD diagnosis: 19 [SD 28.58] years) participated in the patient workshop. They had previously tried a range of topical, phototherapy, and systemic treatments.

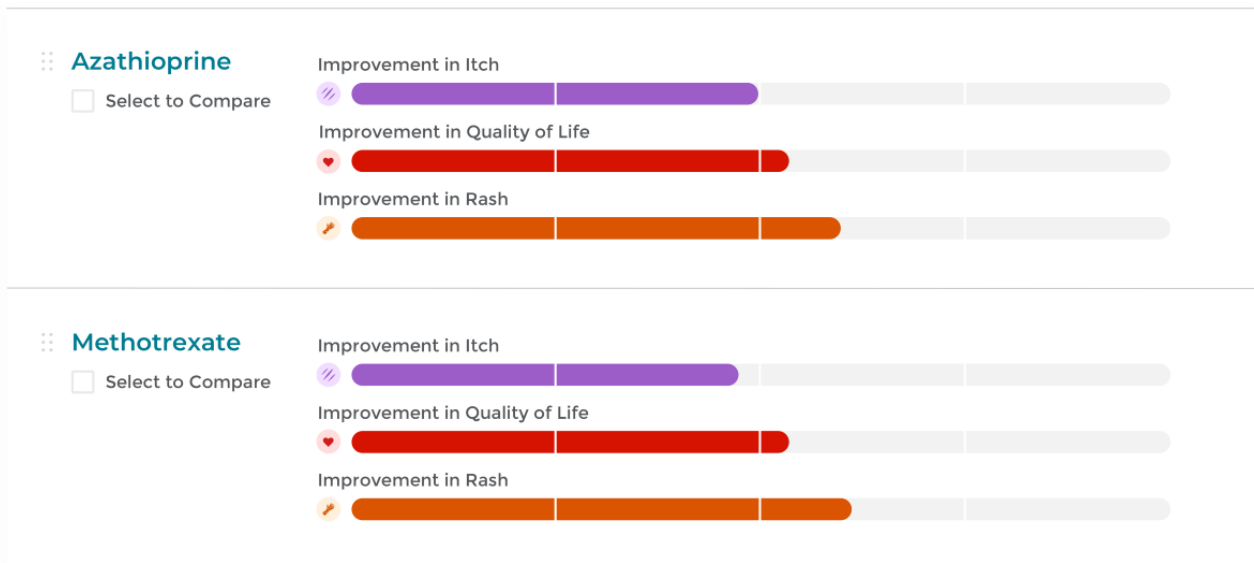
Participants had a range of educational attainment from high school to professional or graduate degrees.

Two digital product designers guided the participants through several sections of the prototype with a focus on their understanding of the various outcome domains (eg, improvement in itch, improvement in quality of life, avoiding potentially

dangerous side effects, etc) for each drug and the visualization of the NMA results. Overall, their feedback was positive; they felt it presented reliable information that gave them hope that more treatments were in the pipeline. They understood the goal of the website and stated that its affiliation with a teaching hospital and listed researchers gave the website more credibility. A high priority for the participants was the ability to see all the results at once without having to preselect individual outcome domains.

Participants had difficulty understanding the meaning of “relative effectiveness” and why each result was linked with a “certainty rating” (based on Grading of Recommendations, Assessment, Development and Evaluations [GRADE]) [14]. Based on their feedback, we changed the wording of “relative effectiveness” to “how do these drugs compare?”. We simplified the workflow of the website so NMA results would be displayed with fewer clicks. We also removed several outcome domains and the certainty information from the patient page (Figure 1).

Figure 1. Visualization of network meta-analysis results from the patient website page. The colored bars represent effectiveness on various outcome domains (ie, itch, quality of life, improvement in rash). Users can also select 2 medications for a more detailed head-to-head comparison.



Clinician Workshop Results

A total of 7 clinicians (mean age 36 [SD 6.05] years; 4/7, 57% female; mean 6 years in independent practice) who treat patients with AD participated in the workshop. Clinicians were all dermatologists working in either academic or community group or solo practices. They reported seeing between 2 and 10 AD patients per month.

They understood both “relative effectiveness” and GRADE certainty information. Similar to patients, they wanted to see all the results at once with as few clicks as possible. They felt reassured that the website clearly states it is not affiliated with pharmaceutical companies. A medium-level priority for them was a request for a drug information card when they clicked on the name of each drug. Overall, they understood the presented results but were uncertain whether the information would be clinically meaningful in their practice because at the time of the workshop there was only one targeted medication approved for AD. They felt it was an easy-to-use resource if they wanted to learn more about new treatments.

Usability Testing Results

A caregiver of a child with AD participated in a remote usability testing session with 2 digital product designers and 1 clinician investigator (AMD). The user’s expectation from the home page was that she would learn more information about eczema research and upcoming clinical trials. She did not have any issues navigating the website and had no difficulty

understanding its content. She believed the longer bars on the “Avoiding potentially dangerous side effects” domain meant more dangerous side effects. The wording was then changed to “Safety: Fewer Serious Adverse Events.”

Discussion

Principal Findings

We created a knowledge translation website for a living network meta-analysis of AD treatments, employing a user-centered design approach and iterative feedback from patients, caregivers, and clinicians. The website [15] was launched in April 2020, and since then, we have posted 6 NMA result updates. According to our website analytics (assessed June 13, 2022), it has been visited 7418 times by users from over 65 countries. There were 887 active users over the previous 30 days, suggesting it has enduring utility.

Our questionnaire found that learning about new AD treatments is a high priority for adults with AD and caregivers of children with AD. Most of the participants expected to learn this information from their physicians, so it is important to disseminate new treatment information to clinicians treating AD. Clinicians were motivated to tell their patients about not-yet-approved treatment options, but many felt that the lack of evidence-based comparisons between treatments can impede care. There was an apparent need among patients and clinicians

for a tool that can help them better understand and compare new AD treatment options.

In workshops, we received overall positive feedback about the website from participants who provided suggestions to improve the usability of the website. Their insights on data visualizations and language contributed to the subsequent interface design. Patients and clinicians were satisfied with similar data visualizations, with some simplification on the patient page. Usability testing with a caregiver found that the final design was easy to navigate and understand.

Our website achieves the following 2 goals of knowledge translation for our NMA results: (1) open science, in which information is disseminated in an available, transparent, and timely manner; and (2) dissemination of useful information to end users (ie, patients and clinicians). Researchers usually rely on passive knowledge translation strategies such as journal publications and conference presentations [16]. Passive knowledge translation approaches are less likely than active knowledge translation approaches to result in uptake of the information and often lack stakeholder engagement. An active knowledge translation approach that involves end users in the development process may lead to better uptake [17].

Other living NMA websites achieve the open science goal of disseminating NMA results. The COVID-NMA Initiative group has developed a living mapping and systematic review of COVID-19 trials [6,7]. Users can use its interface to perform their own meta-analyses using the COVID-NMA's frequently updated database. Similar living NMA websites have developed sophisticated interactive data visualizations, but users without training in NMA methodology may find it difficult to interpret the results [8,9]. Compared to other living NMA websites, our research page is less sophisticated and interactive. Living NMA websites are an improvement over traditional knowledge translation strategies in that they are more efficient at delivering up-to-date information to other researchers, but dissemination and uptake need to reach clinicians and patients in order bridge the gap between science and practice.

Our website was specifically designed to disseminate NMA results to end users, with specific pages dedicated to researchers, patients, and clinicians. Similar to other living NMA websites, our research page posts extensive data from our NMA results.

The patient and clinician pages display the NMA results using easy-to-understand comparative visualizations.

Limitations and Future Directions

For feasibility, patient and caregiver participants were recruited from a single urban tertiary care center in Canada. Clinician survey participants were recruited only from Canada, and clinician workshop participants all worked in the Toronto area. We only conducted final usability testing with a single end user; however, our research team included clinicians and patients who also provided iterative feedback as the website was in development. Our findings may not be fully generalizable to all end users; additional testing with more users on the final website product would be informative.

One of the aims of the website is to provide a treatment comparison tool for patients with AD and clinicians. A user experience study can investigate users' purpose for the website and whether their goals align with those we set out. To further improve user experience, it may be worthwhile to add a short video with an introduction to the website and a basic overview of NMA methodology. Research has found that videos are an effective knowledge translation tool and can lead to overall knowledge improvement [18].

Traditionally, research impact is measured by bibliometric measures such as Impact Factor and citation counts [19]. As open science expands to wider, nonacademic audiences, it may be worthwhile to consider alternative metrics (*altmetrics*) to better capture other forms of dissemination that are more accessible and popular among nonacademic knowledge users [17]. Altmetrics can assess dissemination of research to groups outside the scientific community by aggregating mentions in media outlets such as blogs, forums, discussion sites, and social media such as Twitter and Facebook [17].

Conclusions

To address the need among patients and clinicians for evidence-based information on systemic AD treatments, we developed a website to present results from a living systematic review and NMA. Engaging end users during the design and development process resulted in a tool that makes complex NMA results more relevant to their treatment decision-making process.

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Conflicts of Interest

OM was a paid contracted Digital Product Design Fellow at Healthcare Human Factors with no conflicts of interests to declare. JV (Partner at Thousand Plus Inc) has received compensation on behalf of Thousand Plus Inc from the Women's College Research Institute for the development of the EczemaTherapies website. CF is chief investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a principal investigator in the European Union Horizon 2020-funded BIOMAP Consortium. He also leads the European Union Trans-Foods consortium. His department has received funding from Sanofi-Genzyme and Pfizer for skin microbiome work. AMD has received compensation from the British

Journal of Dermatology (reviewer and section editor), American Academy of Dermatology (guidelines writer), and National Eczema Association (grant reviewer). KPLL, PA, LP, ML, SNV, TC, BWMA, TB, and TM have no conflicts of interests to declare.

Multimedia Appendix 1

Questionnaires.

[[DOCX File, 15 KB - derma_v5i3e41201_app1.docx](#)]

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Abbreviations

AD: atopic dermatitis

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

NMA: network meta-analysis

SUCRA: surface under the cumulative ranking curve

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Review

Emojis and Emoticons in Health Care and Dermatology Communication: Narrative Review

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Abstract

Background: Emoticons and emojis have become staple additions to modern-day communication. These graphical icons are now embedded in daily society through the various forms of popular social media and through users' personal electronic conversations. With ever-increasing use and inclusivity, exploration of the possible health care and dermatology applications of these tools is imperative.

Objective: The goal of this narrative review was to provide and evaluate an up-to-date literature survey examining the utility of emoticons and emojis in medicine. Special attention was paid to their existing and potential uses in the field of dermatology, especially during the COVID-19 pandemic.

Methods: A PubMed search of peer-reviewed publications was performed in mid-2021 to collect articles with emoticon or emoji keywords in combination with other health care-relevant or dermatology-relevant keywords. Screening of publications and described studies was performed by the authors with education and research experience in health care, dermatology, social media, and electronic communication trends. Selected articles were grouped based on common subjects for qualitative analysis and presentation for in-depth discussion.

Results: From this extensive search, researchers were able to identify a wide variety of publications detailing the use of emoticons and emojis in general health care, pediatric health care, public health, and dermatology. Key subject areas that emerged from the investigation included the ability of emoticons and emojis to improve communication within pediatric health care, enhance mood and psychological assessment or mental health screening in adults, develop interventions to improve patient medication adherence, complement novel means of public health and COVID-19 surveillance, and bolster dermatology-specific applications.

Conclusions: This review illuminated the repurposing of emojis and emoticons for a myriad of advantageous functions in health care and public health, with applications studied in many populations and situations. Dermatology-specific uses were relatively sparse in the literature, highlighting potential opportunities for growth in future studies and practices. The importance of diversity and inclusivity has extended to emojis, with the recent introduction of skin color customization and new emojis better representing

the comprehensive spectrum of users' experiences. A continuously evolving and technology-driven population creates a unique niche for emoticons and emojis to ease worldwide communication and understanding, transcending the barriers of age, language, and background. We encourage future studies and innovations to better understand and expand their utility.

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KEYWORDS

emojis; emoticons; dermatology; social media; medicine; public health; COVID-19; narrative review; literature review; mobile phone; Skin of Color

Introduction

In the ever-evolving world of communication technologies, some of the most popular features include the use of emoticons and emojis, more broadly known as “graphicons” or graphical icons [1]. As electronic communication begins to supplant face-to-face communication, these graphicons can convey emotions and compensate for the lack of nonverbal visual cues in computer-based text, such as facial expressions, body language, and tone of voice. Therefore, emoticons and emojis help broker the relationship between messages and their intended meanings [2].

A portmanteau of “emotion” and “icon,” emoticons specifically refer to icons indicating emotional expressions and were first observed on web-based message boards in 1982. Combinations of keyboard letters and symbols can represent an emotional status by depicting a face or body part, such as “:-D” for laughing, or possibly with other accessories and elements of popular culture, such as “*<|;-)” for Santa Claus [3]. A more recent expansion of the emoticons concept occurred with the development of emojis, defined as “a visual representation of an emotion, idea, or symbolism” and can also enhance text-based and web-based communication [4]. The telecommunications interface designer Shigetaka Kurita devised some of the world's first emoji sets in the 1990s, drawing inspiration from Japanese pictograms. It was apparent that without a mechanism such as emojis to provide important contextual information, the rise of electronic text communication would be accompanied by an increase in miscommunication. A popular example of an emoji is the “Face with Tears of Joy” (☺), which was the Oxford Dictionary's Word of the Year in 2015 and remains one of the most commonly used emojis [5]. A recent survey of university students indicated that the overwhelming majority used emojis (91%), most commonly facial expressions, followed by hand gestures, objects, and symbols. They also heavily preferred emojis over emoticons (86%), citing their visual appeal, expressiveness, and ease of use [6]. The use of an image such as an emoji to represent concepts is not a new one. Years of

human history have indicated that imagery is an integral portion of language and communication. The ancient Egyptians used pictographic hieroglyphic symbols as their written language to communicate about items, emotions, and stories [7]. Emoji databases presently contain >2823 unique visual representations of different emotions, actions, foods, sports, items, and other concepts, and this number is constantly growing [3]. The concurrent rise of social media has skyrocketed emoji use into a widespread phenomenon, with billions of emojis exchanged daily on different platforms across all genders and nationalities [8].

With the increasing popularity of emoticons and emojis, as well as their established utility in enhancing human communication, the world of health care must consider their influence and role. Effective exchange of information in health care is paramount, and previous studies have indicated that language-based health assessments can often inadvertently perpetuate biases because of language barriers and lower health literacy. Implementation of image-based surveys using emoticons and emojis may be effective in overcoming or even eliminating these potential biases [9]. In addition, physicians should be aware of their use to cater to younger populations and their preferences for using social media, emojis, and texting slang to communicate. Integration of these modalities into regular practice may help forge important communication avenues and rapport between patients and providers [10]. Along these lines, recent movements have sought to increase diversity and inclusivity in the skin tone of emojis to better represent the user; in 2015, the Unicode Consortium, a nonprofit organization upholding international software standards, worked with Apple developers to release an emojis update featuring 6 different skin tone options based on the Fitzpatrick scale in dermatology (Figure 1) [11,12]. However, the potential implications for dermatologic care and Skin of Color dermatology patients remain unclear. Therefore, this narrative review surveys the existing body of scientific literature on the applications of emoticons and emojis in improving various aspects of health care and dermatology, especially in light of the COVID-19 pandemic, triggering further shifts to electronic communication.

Figure 1. The 6 different skin tone–modifying options for emojis introduced by Apple and the Unicode Consortium in 2015 [11,12].



Methods

A PubMed survey of peer-reviewed publications was conducted from May 2021 to December 2021 to identify articles related to emojis and emoticons in the context of health care, dermatology, and the COVID-19 pandemic. PubMed was chosen to conduct the searches as it has been widely recognized as a pre-eminent public source for searching and accessing biomedical literature [13] and currently indexes citations from >34 million publications and 30,000 scientific journals [14]. It was noted that the terms “emoticons” and “emojis” were often conflated and used interchangeably in the literature, despite the subtle differences in definitions we have described in the *Introduction* section [3]. For simplicity, in this paper, we will henceforth use the term “emojis” to refer to the concepts of both “emoticons” and “emojis.” However, to ensure a comprehensive initial screening, we performed literature searches on both terms using combinations of keywords such as “emoticons,” “emojis,” “social media,” “internet,” “dermatology,” “medicine,” “health,” “health care,” “public health,” “covid,” “COVID-19,” and “SARS-CoV-2.” An initial PubMed search of the terms “emojis” and “emoticons” yielded 225 unique publications, which were examined by researchers with education and experience in health care, dermatology, social media research, and trends in electronic communication who independently screened titles and abstracts of search results for relevance and recency, as well as references to important literature cited by resulted publications. Each potential publication required an individual detailed review by the researchers for inclusion, as emoji-specific Medical Subject Headings terms currently do not exist for indexing of PubMed items, and searches returned multiple publications that included only 1 instance of the

keyword in the full text, such as research regarding restaurant inspection reports or broad studies of social media sentiment analysis outside of the health care and dermatology scope. Exclusions and subject area determinations were confirmed in consultation with a board-certified dermatologist and a prominent researcher with extensive investigative and editorial experience in health care social media. Preprints, duplicate results, and non-English language publications were also excluded. As our aim was to compile a narrative review of the recent literature, the qualitative analysis focused on examining the specific use of emojis, the populations studied, and the proposed generalizability of the findings. Ultimately, a small subset of articles was featured for in-depth discussion, grouped by a selection of overarching subject areas that emerged from the observed patterns in the results related to applications of emojis.

Results

Overview

A selection of 31 recently published articles from studies on general health care, public health, and dermatology was analyzed after screening the emojis literature. We identified several main subject areas, including communication in pediatric health care, assessments of mood and mental health screening in adults, improvements in medication adherence, public health tracking or interventions and COVID-19–related publications, and emoji use in dermatology-specific applications and indicators of skin tone. A narrative review of our findings is detailed in the following sections, organized under the headings of the various article subject groupings. A summary of the study population and type for each examined article is also available in [Table 1](#).

Table 1. Summary of relevant emoticon- and emoji-related articles examined in this narrative review grouped by subject area.

Number	Article title	Year published	Study population	Study type	Summary
Subject Area: Pediatric Health Care					
1	Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients [15]	2010	120 patients in the emergency department; children aged 8 to 17 years	Prospective observational study	Validation of the Wong-Baker FACES Pain Rating Scale and correlation to a pain severity visual analog scale in children presenting to a suburban academic pediatric emergency department with pain
2	Children's self-report of pain intensity: what we know, where we are headed [16]	2009	50 peer-reviewed publications	Literature review	Synopsis of self-reported measures of pain intensity in children, including an overview of principles, measurement issues, and recommendations for clinical practice and further research
3	Use of an animated emoji scale as a novel tool for anxiety assessment in children [17]	2019	102 randomly selected healthy children aged 4 to 14 years visiting an academic pediatric dentistry department in India	Pilot study	Evaluation of a newly designed animated emoji scale to assess dental anxiety in children, with comparisons to the commonly used Venham picture test and facial image scale
4	Emoticon use increases plain milk and vegetable purchase in a school cafeteria without adversely affecting total milk purchase [18]	2015	297 children from an inner-city elementary school in Cincinnati, Ohio, United States	Community trial	Investigation of whether emoticon placement next to healthful foods, particularly plain white fat-free milk, in an elementary school cafeteria would increase healthy purchases
5	The meaning of emoji to describe food experiences in pre-adolescents [19]	2020	254 preadolescents aged 9 to 13 years attending primary and secondary school in Florence, Italy	Cross-sectional study	Investigation of the emotional meanings and word linkages of emoji used to describe food experiences and analysis of age and gender differences
6	Assessing the meaning of emojis for emotional awareness—a pilot study [20]	2019	386 web-based survey respondents	Web-based survey	Investigation of how emotion-related emojis are interpreted by age and gender and assessment of the suitability of emojis in probing for emotional awareness
7	Emoji questionnaires can be used with a range of population segments: findings relating to age, gender and frequency of emoji/emoticon use [21]	2018	1084 urban Chinese consumers from diverse demographic and socioeconomic backgrounds	Web-based survey	Assessment of differences in the interpretation of 33 facial emojis and measurement of emotional associations with consumer food products
8	Potential of using visual imagery to revolutionise measurement of emotional health [22]	2020	N/A ^a	Commentary	Thought piece exploring how digital visual imagery such as emoji could provide more effective measurements of emotional health
Subject Area: Adult Mood and Psychological Assessments					
9	Development and preliminary validation of an image-based instrument to assess depressive symptoms [9]	2019	Recruitment via worldwide web-based social media; study 1: 430 young adults; study 2: 482 young adults	Web-based survey	Assessment of depressive symptoms through web-based surveys using 36 emojis; study 1: investigation of participant mood and behavior over the past week, as depicted by emojis, and correlations with the widely used Center for Epidemiologic Studies Depression Scale self-reports; study 2: evaluation of a 10-emoji subset for validity with self-reported depressive symptoms and Big 5 personality traits
10	Can an emoji a day keep the doctor away? An explorative mixed-methods feasibility study to develop a self-help app for youth with mental health problems [23]	2019	32 participants aged 16 to 24 years receiving care from a psychiatric facility followed over 3 months	Mixed methods feasibility study	Development and evaluation of a new emoji-based digital mental health daily monitoring tool, G-Moji, to assess positive or negative feelings and allow pattern analyses for potential clinical applications

Number	Article title	Year published	Study population	Study type	Summary
11	Depression screening using daily mental-health ratings from a smartphone application for breast cancer patients [24]	2016	78 adult patients with breast cancer in South Korea, generating 5792 total sets of daily mental health ratings over a 48-week period	Pilot study	Evaluation of an emoji-based mobile mental health daily tracking app to screen for and monitor indicators of depression, with comparisons to PHQ-9 ^b screening
12	Sensitivity and specificity analysis: use of emoticon for screening of depression in elderly in Singapore [25]	2018	77 participants aged >65 years recruited from a geriatric outpatient clinic in Singapore	Cross-sectional study	Examination of correlations between mood ratings on an emoji scale and comparisons with DSM-IV ^c assessments
13	Exploring the utility of community-generated social media content for detecting depression: an analytical study on Instagram [26]	2018	749 participants recruited through a web-based crowdsourcing platform	Web-based survey and feature extraction from participants' Instagram profiles	Investigation of community- and self-generated social media content as a depression screening approach and comparisons with clinically validated PHQ-8 ^d questionnaire responses
Subject Area: Medication Adherence					
14	Using conversational agents to explain medication instructions to older adults [27]	2018	360 adult participants in the United States recruited from Amazon Mechanical Turk	Web-based survey and pilot study	Development and assessment of a virtual conversational agent system to encourage patient self-care and deliver medication instructions, including an investigation of how appearance, realism, facial cues, and social responses from the virtual agent affect patient learning
15	Feasibility and acceptability of a digital health intervention to promote engagement in and adherence to medication for opioid use disorder [28]	2021	24 adult participants undergoing outpatient opioid addiction treatment	Semistructured interviews	Evaluation of the effectiveness, acceptability, and structure of a combined computer-delivered and SMS text message-delivered intervention (including emojis) for individuals initiating buprenorphine treatment for opioid use disorder
16	Nudge me: tailoring text messages for prescription adherence through N-of-1 interviews [29]	2021	35 participants with at least one chronic condition treated at a large Colorado health care system	Synchronous video interviews	Evaluation via interviews and content analysis of SMS text messages containing emojis to motivate medication adherence and refills
Subject Area: Public Health and the COVID-19 Pandemic					
17	Frequencies of private mentions and sharing of mammography and breast cancer terms on Facebook: a pilot study [30]	2017	1.1 million unique female Facebook users generating 1.7 million unique interactions	Cross-sectional study	Analysis of terminology and emoji reactions used in popular social media content regarding breast cancer screening and diagnosis by female Facebook users
18	May emoji improve CPR knowledge? [31]	2019	N/A	Commentary	Proposal to add new emojis to the Emoji Unicode List representing the steps of CPR ^e and early defibrillation to increase awareness and knowledge
19	Public awareness, emotional reactions and human mobility in response to the COVID-19 outbreak in China—a population-based ecological study [32]	2020	Mobility data and Weibo social media interactions from 70 million mobile phone users in Sichuan, China	Ecological study	Description and analysis of changes in mobility patterns and public emotional reactions via emojis during the COVID-19 pandemic in early 2020
20	Surveilling COVID-19 emotional contagion on Twitter by sentiment analysis [33]	2021	3,308,476 Tweets on Twitter	Focused social media-based sentiment analysis	Examining the flow and content of Tweets, including emojis; exploring the role of COVID-19 pandemic key events, assessing Twitter as a potential surveillance tool for managing pandemic response, and monitoring the spread of information and emotions throughout a population

Number	Article title	Year published	Study population	Study type	Summary
21	COVID-19 and the gendered use of emojis on Twitter: infodemiology study [34]	2020	50,811,299 Tweets from 11,706,754 unique users	Infodemiology study	Analysis of Tweets on Twitter with the hashtags #Covid19 or #Covid-19 to determine how emojis were used to discuss various pandemic-related topics and examination of differences in emojis used by gender
22	How a smiley protects health: a pilot intervention to improve hand hygiene in hospitals by activating injunctive norms through emoticons [35]	2018	65,907 hand hygiene opportunities and 3340 hand hygiene events at a hospital in Germany	Pilot study	Examination of an emoji-based electronic monitoring and feedback system to reinforce hand sanitizer use by hospital staff in patient rooms, suggesting that activating injunctive norms could improve hand hygiene behavior
23	Emojis in public health and how they might be used for hand hygiene and infection prevention and control [36]	2020	57 peer-reviewed publications	Literature review	Overview of emoji use in medicine and public health and how emojis may be used to improve hand hygiene and infection prevention and control

Subject Area: Emoji Skin Tone and Dermatology-Specific Applications

24	Technically white: emoji skin-tone modifiers as American technoculture [37]	2019	35 articles, blog posts, videos, podcasts, or opinion pieces published after the introduction of emoji skin tone modifiers and 600 associated user comments	Critical technocultural discourse analysis	Exploration of the significance of emojis and the introduction of emoji skin tone modifiers in terms of race and racial representation and as cultural artifacts where the meaning depends on the cultural and technological context
25	The problem with emoji skin tones that no one talks about [38]	2018	N/A	Opinion article	Personal commentary regarding the impact of emoji skin tones on users of various skin tones, suggesting that the 5 possible emoji skin tones still pose limitations and demonstrate a lack of diverse representation
26	Linguistic signaling, emojis, and skin tone in trust games [39]	2020	310 undergraduate volunteers	Between-subjects experiment	Assessment of the impact of emoji use, emoji skin tone, and emoji gender on player trust and communication in laboratory-based trust games on mobile devices
27	Emoji skin tone modifiers: analyzing variation in usage on social media [40]	2020	80,000 Twitter users	Cross-sectional study	Quantitative and qualitative analysis of variation in the use of emoji skin tone modifiers by different subpopulations of Twitter users and associations with their own real-life skin tone, as well as their choices regarding web-based identity expression and how to represent other users
28	The bald emoji effect: alopecia and twitter [41]	2021	1166 tweets, including 808 original tweets	Content analysis	Examination of perceptions of alopecia, hair loss, and related treatments on Twitter; also presenting information about the origin and popularity of the bald emoji
29	Social media as a surveillance tool for monitoring of isotretinoin adverse effects [42]	2020	3082 Instagram posts	Cross-sectional study	Analysis of Instagram posts with hashtag #accutane to survey public attitudes about oral isotretinoin and adverse effects, which corroborated known side effects and could be used for real-time treatment surveillance
30	How do disease perception, treatment features, and dermatologist-patient relationship impact on patients assuming topical treatment? An Italian survey [43]	2015	495 patients with psoriasis at specialized psoriasis hospital centers in Italy	Cross-sectional survey study	Assessment of patient knowledge and attitudes toward psoriasis and treatments via a self-administered questionnaire, including emojis to graphically represent feelings and perceived features of topical therapies

Number	Article title	Year published	Study population	Study type	Summary
31	Validation and banding of the ItchyQuant: a self-report itch severity scale [44]	2017	76 adults with chronic pruritis	Pilot study	Application and investigation of ItchyQuant, an emoji-illustrated numeric rating scale for itch severity, to establish clinical utility, assess patient preferences, and provide validation compared with a traditional numeric rating scale

^aN/A: not applicable.

^bPHQ-9: Patient Health Questionnaire–9 items.

^cDSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.

^dPHQ-8: Patient Health Questionnaire–8 items.

^eCPR: cardiopulmonary resuscitation.

Pediatric Health Care

Emojis have been very effective in communicating with children and promoting healthful behaviors. Such visual imagery offers the potential to augment clinical assessment techniques in children or those with cognitive limitations as it can provide information that other forms of communication cannot. Currently, commonly used assessment methods include numeric rating scales, visual analog scales (eg, where participants can indicate subjective pain levels by making a mark along a horizontal line of fixed length), and verbal rating scales. However, in studies of itch and pain severity measurement, these scales were not as suitable and posed difficulties for young children, older adults, and nonnative English-speakers [44]. Thus, emoji-like facial expression illustrations called “faces scales” were developed to address this need. Each facial expression symbolizes a categorical response arranged in an ordinal manner to represent a spectrum of possibilities within a self-reported measure, such as 0 (smiling face, no pain) or 5 (crying sad face, worst pain). Some variations in face scales exist, and research has established that these are generally the pain reporting methods preferred by children [15,16]. Although these face scales could easily be administered on a tablet, at least one of the studies seemed to administer the scales on a paper form [15].

These face scales have been expanded to incorporate motion emoticons and animated emojis to help overcome major barriers in pediatric patient management, such as dental anxiety in children. Fear of dental visits or unwarranted distress over dental procedures is common and may continue into adulthood, contributing to the neglect of oral health. Therefore, early recognition and assessment of dental anxiety is important to identify those needing special assistance or additional support [17]. A comparison of anxiety scales was undertaken to determine an ideal anxiety scale that was easy and efficient to use clinically, appealing, and applicable to younger children with limited cognition and linguistic ability. A newly designed animated emoji scale tested at dental visits for healthy children aged 4 to 14 years showed a high correlation with other common scales, including a face scale; however, the animated emoji scale displayed on an electronic device was the preferred scale by 75% of children and was the expected preference over paper-printed still cartoons [17].

In another successful application of emojis in serving pediatric populations, an inner-city elementary school cafeteria labeled

healthy foods with green smiley face emoticons printed on nearby signs and discovered significant increases in children’s selection of plain fat-free milk over chocolate milk, as well as significant elevations in vegetable purchases [18]. Emojis have also been used more generally to help preadolescents describe emotions and experiences associated with food, and gender and age differences were found in how participants discriminated between emojis representing nuances of meaning. Although categories of emotions for children were quite broad initially, they began to narrow during the preschool years, with girls and older children (aged 12–13 years) eventually demonstrating higher levels of understanding when interpreting variations in emotions compared with boys and younger children (aged 9–11 years), particularly when distinguishing different positive expressions [19]. The ability to discriminate among emotions continued to increase with age, whereas gender differences persisted. Familiarity and frequency of emoji use remained higher among women compared with men [19]. However, certain emojis showed greater consensus and high agreement in meaning, such as the aforementioned popular “face with tears of joy” (😄), “pouting face” (😏), “crying face” (😭), “face with open mouth” or surprised face (😮), and “neutral face” (😐) [20]. Furthermore, other studies have found that gender and age differences in the interpretation of emojis became negligible for adults answering emoji questionnaires [21]. Challenges continue to exist surrounding the interpretation of images across different cultures, generations, and demographic groups; thus, further broad investigation is recommended to ensure reliable and valid results in clinical assessments [22].

Adult Mood and Psychological Assessments

There is also extensive documented use of emojis in mood and psychological assessments for adult populations. Well-validated questionnaires exist for the screening of many conditions such as depression; however, all text-based items that rely on verbal queries are prone to significant bias. Differing education levels and variations in a participant’s primary language can create accessibility barriers to these screening methods [9]. Therefore, nonverbal and image-based approaches that are independent of language, such as emojis, were studied as alternative screening tools. A sample of 482 young adults evaluated an emoji-based 10-item assessment performed on the participants’ PCs or smart devices, with the following directions: “Below is a list of emoji depicting some of the ways you may have felt or behaved. Please indicate if each of the following was true for you much of the

time during the past week.” The survey was internally consistent with high sensitivity for screening depression but showed only moderate specificity. Although promising, further validation may be required before truly language-free emoji-based items can replace conventional instruments [9].

The developers of a mobile health app called “G-Moji” extended this approach of using emojis for psychological assessment. In a feasibility study [23], youth and young adults were able to select 1 of the 14 emojis in response to a daily short survey question in the mobile app, “How are you feeling today?” Call logs, location, phone activity levels, app use, social media interactions, and daily routines were passively collected by G-Moji to obtain environmental or sociobehavioral data and contextualize participants’ responses. Participant feedback was used to further improve and develop the apps. All participants agreed that mobile apps such as G-Moji have the potential to build individual awareness of their own behavioral patterns and changes between positive and negative feelings, with the possibility of motivating beneficial lifestyle changes in response. However, these perceived benefits may quickly dissipate for those with severe mental health difficulties, such as struggles with self-harm. Despite this, participants were not observed overall to consider their own feelings more than usual after using the app [23]. Although favorable as a novel way of assessing mental health issues, subsequent investigation of G-Moji is required (with the integration of other collected metrics, which were not analyzed) before its implementation for clinical purposes.

Another mobile mental health daily tracking app was tested in 78 adult patients with breast cancer who reported sleep satisfaction, mood, and anxiety levels as indicators of potential depression over 48 weeks [24]. Participants selected facial emojis arranged on a numeric scale to report their daily ratings of each metric, whereas the validated and commonly used Patient Health Questionnaire (PHQ)–9 items for depression screening was administered biweekly. The performance of the app was comparable with that of the PHQ–9 items screening. Higher adherence to app use was associated with higher screening accuracy. Therefore, accessible and enjoyable approaches to mental health screening demanding minimal cognitive effort, such as emojis, may be less burdensome alternatives for vulnerable participants [24].

Similar findings were observed in a cross-sectional study of mood emoji scales in an older patient population, where hearing impairment or limited language proficiency posed difficulties when other mental health screening methods were used [25]. Participants were asked, “Which of these faces describe your mood over the past 1 week?”; after this question, participants rated their moods using an emoji scale presented by the interviewer. The emoji scale ranged from 1 (most happy face) to 7 (most sad face), which was compared with the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) criteria assessments. Although the sensitivity and specificity of the scale could be improved, it was simple and easy to use, and participants did not exhibit any difficulty in comprehending the questions or differentiating emotions [25].

Emojis can also contribute to the prediction and tracking of depression in communities through social media. A web-based survey study published in the *Journal of Medical Internet Research* recruited 749 participants for depression screening and granted researchers access to their Instagram social media profiles, thereby capturing participants’ posts, captions, and comments [26]. Although previous studies had focused on screening only user-generated social media (including Facebook and Twitter) content created directly by the participant, this study also analyzed community-generated content such as a user’s followers and friends’ responses to the user through received “likes” and comments. Clinically validated PHQ–8 items questionnaire responses were used as reference standards. Various features were extracted from Instagram data to develop a predictive framework with linguistic components, multiple ratings of general user sentiment, and emoji scores. Elastic net regularized linear regression models were then trained to predict PHQ–8 items scores. User-generated and community-generated Instagram content was found to be nonoverlapping, and statistical tests indicated that combining these complementary sources was the most accurate in detecting depression. This suggests that examining social media interactions, including consideration of used emojis, can provide valuable mental health information and play a role in future mental health risk assessment and intervention strategies [26].

Medication Adherence

It is evident that emojis, whether intentionally created for this purpose, are finding a way into more areas of life than just electronic messaging. Another promising application has emerged in the improvement of health care delivery by increasing medication adherence—the extent to which an individual’s medication use corresponds to their health care provider’s recommendations. As rates of chronic illness and demands of self-care and medication use increase with age, effective modalities for communicating complex medical information and providing instruction to older adults are paramount [27]. On average, medication adherence is quite poor, only approximately 50% for patients with chronic conditions, and is responsible for a substantial proportion of hospital admissions or deaths and health care costs in the United States. Face-to-face communication with health care providers has traditionally been the primary avenue of delivery, especially for older adult patients, which allows the presentation of both verbal and nonverbal (eg, tone of voice and facial expressions) information. This is beneficial for patient retention of instructions [27]. However, inconsistencies in this approach and increasing reliance on digital platforms have led to the exploration of electronically based systems, many of which use emojis.

In one study, a “computer agent” virtual provider was assessed for its ability to deliver medication information to adults [27]. Different levels of realism (photorealism, cartoons, or emojis) in the appearance of the computer agent were tested. Nonverbal and verbal cues were combined in an attempt to elicit social responses from the human participants. Interestingly, the varying degrees of realism were not significantly associated with participants’ memory of the medication messaging, although realistic and cartoon agents received slightly better favorable

evaluations than emoji agents and were perceived as more human [27].

The incorporation of emojis into patients' personalized feedback messages assisted in improving buprenorphine adherence and intervention engagement in a group of 24 adults undergoing outpatient addiction treatment [28]. Trained interviewers surveyed the group for their preferences regarding a new 8-week interactive SMS text message-based digital health program in a qualitative study. Almost all participants reported a desire for the messages to feel more personal by including multimedia elements such as emojis, animations, and videos. Reasons shared included "because then you feel like you're talking to a real person" and "an emoji ruler's cool 'cause that's more eye catchin.'" The more personalized and less generic the messages seemed, the more motivating the intervention was perceived to be. It was also generally acknowledged that younger participants may be more receptive to multimedia features [28].

However, another study found that both younger and older respondents reacted unfavorably when emojis were used in SMS text messages that encouraged timely prescription medication refills [29]. In total, 35 English- and Spanish-speaking patients being treated for at least one chronic condition in a large health care system were interviewed for feedback about the design of the interactive SMS text message intervention. Participants were of diverse ages and ethnic backgrounds and were prompted to choose from different versions of SMS text messages, some of which included emojis, slogans, and variations in the use of abbreviations and message length. Younger respondents noted that the use of emojis felt like the researchers were "trying too hard," whereas older patients reported feeling confused by emojis [29]. Thus, it appears that further research is needed with larger numbers of participants to elucidate whether using emojis in messages can affect behavior modification strategies surrounding medication adherence.

Public Health and the COVID-19 Pandemic

Emojis may also offer insights into the perceptions and values of populations when tracking trends in public health. For example, a survey of >1.7 million distinct, breast cancer screening keyword-related Facebook interactions and reactions, including emojis, revealed that 1.1 million unique female Facebook users had contributed in the space of 1 month in 2016 [30]. The most frequently used terms or phrases and shared website links were aggregated according to content, keyword prevalence, age group, and subtotals based on day, among other metrics. The top content category for interactions (36%) was breast cancer-related e-commerce, including both for-profit and nonprofit organization websites selling items connected to breast cancer themes; this content was also the most reshared with users. The second most popular category was celebrity content (26%) commonly originating from television programs, and almost all of these Facebook interactions were emoji reactions to the post. The next largest category was advocacy and charity websites, such as the American Cancer Society donation page. A particular lack of interest in celebrity-driven content was noted among older users, whereas a consistent subgroup of women was responsible for certain popular content with keywords such as "mammogram" [30]. Although this study

presented only a limited snapshot of data, it is clear that social media conversations involving emoji reactions and other elements can provide valuable data when attempting to understand current public attitudes and information sources regarding different diseases.

As in previous health care applications, emojis have been used effectively for educational purposes in public health. A proposal to introduce specific new Unicode emojis for cardiopulmonary resuscitation (CPR) was instigated after bystander response time was identified as a crucial factor in improving extrahospital cardiac arrest outcomes [31]. Therefore, given the prevalence of emoji-heavy social media and electronic communication in daily life, the inclusion of new emojis illustrating the CPR rescue chain presents an opportunity to spread awareness about cardiac arrest safety to the public, overcome any language or cultural barriers, and allow for better retention of knowledge. The proposed CPR-related emojis encompassed 6 actions and 2 symbols: an unresponsive person not breathing normally, rescue breaths, 2 emojis depicting chest compression, and 3 indicating the correct sites of defibrillation paddle application along with the presence of an automated external defibrillator and a semiautomatic defibrillator. The addition of these to the Emoji Unicode List would allow the emoji to be used across operating systems and among both electronic and print resources. The easy visualization and cognitive understanding of these symbols have the potential to advance the representation of written and graphical (images and video) information [31].

Emojis have been instrumental in communication during the COVID-19 pandemic, which has affected the lives of nearly everyone, including hundreds of millions worldwide who have been infected by the virus. Emoji tracking of public sentiment during the pandemic was performed, with interesting results. A study of social media in China found that negative emojis were most prominent in January 2020, when the official declaration of human-to-human transmission was made but before the exponential rise in COVID-19 cases occurred. These decreased as COVID-19 cases increased, whereas anger appeared to be expressed most frequently in March 2020 [32]. These emoji data suggest a link between public awareness of the virus and the emotional state of the population, perhaps providing real-time indicators of mental health. Another analysis of the COVID-19 pandemic's initial emotional impact examined Twitter and categorized the user content as "positive" or "negative." Similarly, it was noted that Twitter discussions became increasingly negative beginning in January 2020 following the World Health Organization's report on COVID-19 transmission, and that sentiment was prone to amplification after key events [33]. Demographic differences also exist in pandemic-related emoji social media discourse. An evaluation of 50 million #Covid-19 and #Covid19 Twitter posts in 2020 found that although the exchanged emojis generally expressed positive sentiments, the discourse surrounding men was significantly more positive than the discourse surrounding women and sexual or gender minorities [34]. Conversely, emojis referencing death and emergency such as the coffin (☠️), skull (💀), and siren (🚨) emojis were found much more commonly in male Twitter discourse. The study suggested that this could

be related to differences in perceived severity of COVID-19 and higher mortality in men. The laptop (🖥️) emoji, which was often used to represent changes from in-person to web-based work, was more common in discourse concerning women. Unique gender-specific emojis were also noted, such as the yoga (🧘), weight lifting (🏋️), or running (🏃) emojis being more frequent in tweets related to women than in those related to men, potentially indicating a higher level of concern by women to exercise and maintain physical health during the pandemic. Therefore, emojis can furnish novel methods for rapid demographic analysis in crisis settings and provide a greater understanding of how emoji use could signify or perpetuate gender roles and differential burdens [34].

Emojis may also assist in hand hygiene, which is a critical element of infection control. Potential tools to improve hand hygiene compliance have explored emojis as part of multimodal educational approaches to simplify instructions, eliminate the need for language translation, and decrease possible misinterpretations of recommendations. Emojis have already been shown to improve hand hygiene behavior in hospital settings. Compared with 3 other tested conditions, an emoticon-based feedback system targeting social norms was found to significantly increase the use of alcohol-based hand rub dispensers [35]. Motion sensors detecting patient room traffic alerted the linked dispenser to possible hand hygiene opportunities for the health care providers. A smiley face (conveying social approval) was displayed on the dispenser's electronic screen when the provider used the dispenser, whereas a frowny face (social disapproval) appeared when the provider did not. Instant feedback and constant monitoring with visual cues were effective in modifying the behaviors. Moreover, dispensers modified to include this electronic emoji screen were used more than twice as much as dispensers in other rooms [35]. However, adherence to simple hygiene procedures was generally difficult, despite numerous intervention strategies attempting to overcome behavioral obstacles [36]. Currently, there is no emoji that directly shows hand washing or hand sanitization. Using a sequence of existing emojis such as “clapping hands” (👏) and “bar of soap” (🧼) can be cumbersome and create confusing misinterpretations such as applauding the use of soap. Introducing new highly specific emojis may be helpful in the universal dissemination of infection prevention education [36].

Emoji Skin Tone and Dermatology-Specific Applications

Despite recent efforts to increase diversity and inclusivity through emojis that represent different skin tones, dermatology-specific applications of emojis have been relatively rare. Early emoji sets faced intense backlash from users with Skin of Color because of the marked absence of diverse emoji characters depicting human figures or body parts. Emojis showed largely only White skin tones and, later, “non-human” unnatural yellow skin colors with no customization options. The resulting public pressure eventually prompted Apple and the Unicode Consortium to release an update in 2015 adding skin tone modifiers (Figure 1). The “blank” emoji without skin tone modification is a yellow nonclassified tone, whereas the

lightest option is meant to encompass the Fitzpatrick skin type 1 or 2. The remaining options denote one of the Fitzpatrick skin types from 3 to 6. Hair texture options were subsequently expanded in 2018 [37]. However, it has been suggested that adding an element of race or ethnicity to emojis posed a disruption of any original intention to be “raceless” neutral symbols and a requirement of shared cultural context for interpretability [37]. It was also speculated that the new explicit visibility of “whiteness” in emojis created tension for users, regardless of racial self-identity. Some users argued that allowing people to “opt in” for skin tones was never a good solution for true representation. Layering a skin tone on top of a previously designed emoji was construed as akin to white emojis simply “wearing masks” [38]. Concerningly, recent experiments have found that although emojis increased trust among players of a mobile messaging trust game, both light skin and dark skin recipients of dark skin emojis reported significant decreases in trust, suggesting that complex social judgments can be associated with emoji use [39]. However, another study found that using opposite-toned emojis on Twitter demonstrated no evidence of negative racial sentiment. The overwhelming majority of used emoji skin tones matched the skin tone of the user's profile photo, and users with darker-skinned profile photos were more likely to use emoji skin tone modifiers overall [40]. Thus, although skin tone emojis have attempted to bolster representation, they have also created an avenue for asking difficult questions about what it means to perform a certain identity with emojis and address the intrinsic power dynamics triggered by their use [37].

Nevertheless, the ability to self-identify skin color holds great potential for patient care in dermatology. It has been established that emojis validating a user's life experiences can be powerful tools for conveying shared emotions and vulnerability. In 2018, a patient with alopecia areata aged 24 years initiated a petition for new emojis to capture her thoughts and feelings, stating “emoji are often used when you don't know the words to say and when you suffer from hair loss it's hard to express yourself...if people were able to use one, it would speak volumes” [41]. The bald emoji (🦋) was introduced and became the most popular new emoji of 2018, suggesting that this sentiment was strongly shared by other patients with alopecia who now felt more included on social media platforms [41]. This led to a surge of tweets on the topic, most of which were related to personal experiences, and also educated users about the condition and its symptoms. However, alopecia advertisements promoting hair growth products, wigs, and hair transplantation were also common, potentially propagating misleading treatment information [41].

Although users should approach accessing social media for medical information with caution, user-generated content, including emojis, may be used to monitor the side effects of dermatologic treatment. Although they did not specifically examine emojis, one study analyzed Instagram posts related to the hashtag #accutane and identified users of the medication. The social media-reported side effects of the drug were similar to the known side effects, as well as the general pattern of the treatment's adverse events. Therefore, emojis in dermatology social media posts can be used as expressive tools for real-time

treatment surveillance [42]. Another area in which emojis can be used in dermatology is for patients to describe their feelings regarding treatment in a clinical setting. Self-administered questionnaires from hundreds of patients with psoriasis at specialized hospitals in Italy revealed that emoticons helped patients express the therapeutic features that were perceived as the most important or distressing. Various emoticons corresponding to descriptors, such as “soothing,” “reliable,” “greased,” “bedaubing,” and “sticky,” were used with respect to different topical therapy formulations [43]. In similar studies on chronic pruritus, patients of dermatology preferred self-reporting their itch symptoms with a cartoon emoji-based scale called “ItchyQuant” over a purely numerical scale or other quantitative scales. ItchyQuant was administered at either the beginning or end of the patient’s clinic visit. The cartoons represented an increasing amount of itch by the changing facial expressions and the amount of scratching. The ItchyQuant measures demonstrated high concurrence with traditional itch severity scales and were clinically meaningful [44]. Given the substantial negative emotional and psychosocial effects of chronic pruritus, emojis could be valuable tools for assessing challenging dermatologic populations with communication barriers, as was the case in other health care fields. Dermatologists should be aware of emoji applications when approaching different conditions that pertain to their patients to navigate the best personalized care for their dermatological needs.

Discussion

Principal Findings

Clearly, emojis can be leveraged and repurposed to fulfill different needs in health care settings. Using emojis can help foster better interactions, including patient-provider relationships, and aid in meeting patients at their preferred level of understanding or cognition. We must take advantage of these novel means to better communicate with patients, as communication is often the largest obstacle to appropriate and comprehensive care, aside from cost [45]. Although imagery such as emojis has been found to yield reliable results in clinical assessments, challenges still exist surrounding their interpretation across cultures and age groups. Therefore, a broad investigative task is ahead to gain a firmer understanding of this and any evolving elasticity of their meaning to different populations [22]. The limitations of our narrative review include the exploratory nature of the search and general exclusion of publications and journals not indexed in PubMed. For example, an important study in a psychological journal not indexed by PubMed [46] by the authors of previously discussed work [9] established the rationale for the suggested linkage of an individual’s self-identification with various emojis and correlations with certain Big 5 personality traits. This highlights another potential use of emojis in the health care space, and future reviews should build upon our initial survey to assess a broader scope of literature.

Nevertheless, current applications of emojis in dermatology are relatively sparse, which is disappointing, given their extensive potential. Our study found that the main clinical applications

for emojis specifically within the field of dermatology were limited to expressing attitudes regarding topicals for psoriasis [43] and using emoji-based cartoons to self-report pruritus severity using the ItchyQuant scale [44]. With recent skin tone modifier updates, patients of dermatology could use emojis to self-identify their skin color and help translate their selection into an accurate Fitzpatrick skin type classification, as this was the basis for Apple’s skin tone options. As was performed with ItchyQuant, emojis could be incorporated into practice during pediatric dermatologic encounters for itch and pain, among other symptoms. This could create a more positive and friendly environment for patients, as it can be challenging to communicate with pediatric patients effectively. The psychosocial and emotional aspects of a pediatric or adult patient’s experience could be easily screened at the dermatology office, perhaps using one of the aforementioned mental health-oriented applications [9]. Patients would be able to self-select emojis that describe their mood or thoughts about their condition and treatment. Going a step further, emojis could also be used as a means of patient satisfaction ranking. As health care expectations, reimbursement, and improvements increasingly focus on the quality of care received, offering an accessible variety of emojis to collect feedback quickly could be effective. Difficult or complex dermatology medication instructions and routes of administration can also be simplified using emojis, for example, assigning day or night use, as well as body area and frequency.

As the world continues to progress through a pandemic, forcing many people to turn to virtual formats and telemedicine as safer choices, more advancements in these communication methods must be implemented and used. There is potential for providers and patients to communicate through emoji-enhanced messages, and in dermatology, emojis can complement messaging about lesions, colors, and symptoms, allowing ancillary information to be sent along with chief concerns. However, although the flexibility and ease of emojis may account for a large part of their appeal [5], emoji use in health care communication may also trigger potential medicolegal implications because of their inherent ambiguity of meaning.

With the continued growth of electronic communication, new applications for emojis may emerge. Although our survey was limited by the simplified search strategy highlighting only a few overarching subjects in previous literature, the dynamic rapid nature of social media and internet trends also entails that this growth will inevitably outpace scientific publications. This solidifies the need for subsequent periodic surveys of emoji-focused studies such as this one. The landscape of emojis is also dynamic, and new emojis, such as skin tone customizations and bald emojis, are continuously introduced and approved. Recent efforts by the medical community to better serve the field have led to the approval of new emojis such as the anatomical heart and anatomical lung, and a more comprehensive set of emojis could be highly beneficial [47]. The current lack of medical emojis presents an important window of opportunity for clinicians and researchers to work toward a consensus and shape an optimized future for this communication modality. For example, dermatologists could introduce specific emojis to illustrate sun safety and sunscreen

use for skin cancer prevention. Emojis to encourage melanoma awareness could be used in conjunction with current skin tone emojis to share information about skin health, thereby helping to address questions about sunscreen being unnecessary for darker skin. Creative applications, including displaying smiley or frowny social approval emoticons [35] on public sunscreen dispensers, could also be potentially effective in increasing dispenser use and positive reinforcement.

Conclusions

The brisk evolution of modern technologies is continuously shaping our lives and health behaviors. The incorporation of

emojis into communication has improved pediatric medicine, adult mood and psychological assessments, medication adherence, and public health tracking and interventions before and during the COVID-19 pandemic. Integration into dermatology practice has so far been limited but is ripe for expansion. Examining the surge in electronic communication that reaches new heights during the pandemic will be crucial to the continued advancement of health care. We aim to spark further innovation by highlighting the recent use and emerging ideas for emoji applications, and it will be intriguing to investigate future developments.

Conflicts of Interest

RPD is the Editor in Chief of *JMIR Dermatology*, Joint Coordinating Editor for *Cochrane Skin*, a dermatology section editor for *UpToDate*, a Social Media Editor for the *Journal of the American Academy of Dermatology*, a Podcast Editor for the *Journal of Investigative Dermatology*, and a coordinating editor representative of the Cochrane Council.

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Abbreviations

CPR: cardiopulmonary resuscitation

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition

PHQ: Patient Health Questionnaire

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Research Letter

From the Cochrane Library: Dietary Supplements for Established Atopic Eczema

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atopic dermatitis, dietary supplements, atopy; fish oil, systemic review; atopic eczema; eczema; probiotics

Atopic eczema (AE) is a chronic inflammatory skin condition, affecting 5% to 20% of people worldwide [1]. While there are many available treatment options that help improve AE, patients for whom these treatments did not work, or who fear side effects, may look to nutritional supplements as “natural” solutions. Nutritional supplements represent a vast, growing industry, globally valued at over US \$150 billion in 2021. Nutritional supplements are manufactured pills, powders, or liquids, meant to provide nutrients in addition to conventional food. Supplements are classified by the Food and Drug Administration as foods rather than drugs; therefore, they are not required to prove efficacy or safety prior to entering the market. Given the growing popularity of supplements, physicians must be knowledgeable about supplement ingredients when counseling patients. A 2012 Cochrane review, “Dietary supplements for established atopic eczema” [1], offers a comprehensive review of evidence regarding popular dietary supplements used in AE. Here, we discuss the findings of this Cochrane review and of relevant subsequent publications. Of note, although food allergies often coexist in patients with AE, supplements were studied for their effects on AE and not as treatments for food allergies.

The review [1] extracted data and assessed the quality of 11 randomized controlled trials, with a total of 596 participants, investigating therapeutic interventions of fish oil, zinc, selenium, vitamin D, vitamin E, vitamin B6, sea buckthorn oil, hempseed oil, and sunflower oil, versus placebo. Participants had physician-diagnosed AE, with 8 studies using the Hanifin and/or Rajka criteria; the other 3 studies did not state a diagnostic method. The authors evaluated evidence of symptom

improvement in the short term, reduced number of flares in the long term, and a reduced need for treatment in the long term.

Overall, there was scarce evidence supporting the use of supplements for treating AE. However, given that many of the included studies were either underpowered or of low quality, evidence was insufficient to claim all supplements are completely ineffective. Nevertheless, the authors advised against further research without a stronger rationale—to the exclusion of fish oil, for which pooled data from 2 small studies suggest it may improve subjective daily quality of life in people with AE [1]. Further research on fish oil is warranted, with preliminary evidence suggesting it may down-regulate inflammation. A 2018 animal study demonstrated that n-3 polyunsaturated fatty acids depressed inflammasome activation, with a resultant reduction in inflammatory cytokine release and overall inflammatory response, as well as marked attenuation of atopic skin lesions [2]. Additionally, a 2018 cross-sectional survey found that 35% of patients who added fish oil to their diet reported an improvement in their AE symptoms [3].

In a 2018 review of probiotics, vitamins, oils, and traditional Ayurvedic agents, there was insufficient evidence to recommend any oral supplements as treatment, with the exclusion of probiotics [4]. Meta-analyses of probiotics have produced conflicting results; variable patient populations, probiotic strains, dosing, and duration of therapy among studies limit the pooling of data for a meta-analysis. Additional large-scale clinical trials are necessary to fully understand the benefits of probiotics for AEs, elucidate optimal strains, and determine which patient populations would achieve the greatest benefit.

Overall, this review highlights the limited evidence that exists for the use of nutritional supplements in AE. At present, the most effective “natural” modality for AE is topical emollients [5]. Future randomized controlled trials of promising dietary supplements should include patient-reported outcomes to fully assess the impact of nutritional modifications.

Conflicts of Interest

RPD is a joint coordinating editor for *Cochrane Skin*, editor-in-chief of *JMIR Dermatology*, a dermatology section editor for *UpToDate*, a social media editor for the *Journal of the American Academy of Dermatology*, and a podcast editor for the *Journal of Investigative Dermatology* (JID). He is a coordinating editor representative on Cochrane Council. TES is an editorial board member-at-large for *JMIR Dermatology*.

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Abbreviations

AE: atopic eczema

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Research Letter

From the Cochrane Library: Interventions for Cellulitis and Erysipelas

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erysipelas; cellulitis; cephalosporins; penicillin; macrolides; intervention; dermatology; skin and soft tissue infections; infection; skin; antibiotics; soft tissue; treatment; therapy; bacterial infection

Cellulitis and erysipelas are types of skin and soft tissue infections (SSTIs) that occur when bacteria, commonly group A beta-hemolytic *Streptococcus* and *Staphylococcus*, enter through breaks in the skin. Cellulitis infects the dermis and subcutaneous fat, while erysipelas is a more superficial variant, affecting the superficial dermal lymphatics and adjacent tissues. Untreated, these conditions may result in life-threatening conditions including sepsis, gangrene, or necrotizing fasciitis [1]. Due to the potential risks associated with these conditions, evidence-based research to inform up-to-date treatment guidelines is critical; Table 1 provides guidelines for reference.

A 2010 Cochrane Review [1], “Interventions for Cellulitis and Erysipelas,” assessed 25 randomized controlled trials comparing treatments for primary skin infections, involving a total of 2488 participants. Specifically, the included trials each compared two or more interventions (eg, antibiotics, such as penicillin, macrolides/streptogramins, or cephalosporins, and steroids), routes of administration, and therapy durations. The objective of the review was to assess the efficacy of interventions for nonsurgically acquired SSTIs. This letter will address the limitations of the original review and provide updates based on recent studies.

Macrolides and streptogramins proved superior to penicillin antibiotics in eliminating or reducing cellulitis symptoms (N=2488). Trials comparing oral macrolides against intravenous penicillin found the former to be superior (n=419). No significant differences were found in studies comparing penicillin to cephalosporins (n=88) or among cephalosporin

generations (n=538). These comparisons are summarized in Table 2.

Notably, the review [1] highlights a lack of evidence regarding the incorporation of corticosteroids into the antibiotic therapy regimen, whereas subsequent studies have suggested a benefit. The Infectious Disease Society of America states that systemic corticosteroids should be considered in nondiabetic adults to hasten the clinical improvement of cellulitis [2]. A 2018 study [3] assessing corticosteroids (0.5 mg/kg prednisone for 2-3 days) as an add-on therapy to antibiotics for patients hospitalized with erysipelas found that adding steroids resulted in quicker recovery rates and return to full function, with less risk of recurrence [4]. A study of 43 children admitted to the hospital for orbital cellulitis reported a 3-day decrease in length of stay for those treated with adjunctive intravenous dexamethasone (0.3 mg/kg/d every 6 hours for 3 days) compared to those treated with antibiotic monotherapy [3].

Notably, the review [1] did not examine the effectiveness of prophylaxis for cellulitis recurrence; the annual recurrence rate is approximately 8% to 20%. In patients with frequent cellulitis recurrence (3-4 episodes annually), erythromycin, intramuscular penicillin, and oral penicillin VK have been posited as appropriate prophylactic options. A 2021 meta-analysis assessing the use of erythromycin and penicillin found a 69% decreased risk of recurrent cellulitis versus placebo and improved recurrence interval. Penicillin was preferred over erythromycin due to its superior tolerability and cost [5].

Table 1. Current Infectious Diseases Society of America guidelines for the management of nonpurulent cellulitis and erysipelas.^a

Disease entity and antibiotic	Dosage, adults	Dosage, children	Comment
MSSA^b SSTI^c			
Nafcillin or oxacillin	1-2 g every 4 h IV ^d	100-150 mg/kg/d in 4 divided doses	Inactive against MRSA ^e
Cefazolin	1 g every 8 h IV	50 mg/kg/d in 3 divided doses	For penicillin-allergic patients, except those with immediate hypersensitivity reactions; more convenient than nafcillin with less bone marrow suppression
Clindamycin	600 mg every 8 h IV or 300-450 mg 4 times daily by mouth	25-40 mg/kg/d in 3 divided doses IV or 25-30 mg/kg/d in 3 divided doses by mouth	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA
Dicloxacillin	500 mg 4 times daily by mouth	25-50 mg/kg/d in 4 divided doses by mouth	Oral agent of choice for methicillin-susceptible strains in adults; rarely used in pediatrics
Cephalexin	500 mg 4 times daily by mouth	25-50 mg/kg/d 4 divided doses by mouth	For penicillin-allergic patients except those with immediate hypersensitivity reactions; the availability of a suspension and requirement for less frequent dosing
Doxycycline, minocycline	100 mg twice daily by mouth	Not recommended for age <8 y	Bacteriostatic; limited recent clinical experience
Trimethoprim-sulfamethoxazole	1-2 double-strength tablets twice daily by mouth	8-12 mg/kg (based on trimethoprim component) in either 4 divided doses IV or 2 divided doses by mouth	Bactericidal; efficacy poorly documented
MRSA SSTI			
Vancomycin	30 mg/kg/d in 2 divided doses IV	40 mg/kg/d in 4 divided doses IV	For penicillin-allergic patients; parenteral drug of choice for treatment of infections caused by MRSA
Linezolid	600 mg every 12 h IV or 600 mg twice daily by mouth	10 mg/kg every 12 h IV or by mouth for children <12 y	Bacteriostatic; limited clinical experience; no cross-resistance with other antibiotic classes; costly
Clindamycin	600 mg every 8 h IV or 300-450 mg 4 times daily by mouth	25-40 mg/kg/d in 3 divided doses IV or 30-40 mg/kg/d in 3 divided doses by mouth	Bacteriostatic; potential of cross-resistance and emergence of resistance in erythromycin-resistant strains; inducible resistance in MRSA; important option for pediatrics
Daptomycin	4 mg/kg every 24 h IV	N/A ^f	Bactericidal; possible myopathy
Ceftaroline	600 mg twice daily IV	N/A	Bactericidal
Doxycycline, minocycline	100 mg twice daily by mouth	Not recommended for age <8 y	Bacteriostatic; limited recent clinical experience
Trimethoprim-sulfamethoxazole	1-2 double-strength tablets twice daily by mouth	8-12 mg/kg/d (based on trimethoprim component) in either 4 divided doses IV or 2 divided doses by mouth	Bactericidal; limited published efficacy data
Streptococcal skin infections	Penicillin: 2-4 million units every 4-6 h IV; Clindamycin: 600-900 mg every 8 h IV; Nafcillin: 1-2 g every 4-6 h IV; Cefazolin: 1 g every 8 h IV; Penicillin: VK 250-500 mg every 6 h by mouth; Cephalexin 500 mg every 6 h by mouth	Penicillin: 60,000-100,000 units/kg/dose every 6 h; 10-13 mg/kg dose every 8 h IV; 50 mg/kg/dose every 6 h; 33 mg/kg/dose every 8 h IV	N/A

^aRecommendation according to the Infectious Diseases Society of America. Doses listed are not appropriate for neonates. Infection due to *Staphylococcus* and *Streptococcus* species. Duration of therapy is 7 days depending on the clinical response.

^bMSSA: methicillin-susceptible *Staphylococcus aureus*.

^cSSTI: skin and soft tissue infection.

^dIV: intravenous.

^eMRSA: methicillin-resistant *Staphylococcus aureus*.

^fN/A: not applicable.

Table 2. Treatment comparison with respective results, risk ratio, and CI.^a

Comparison	Measurement	Results	RR ^b (95% CI)	Studies, n	Patients, n
Macrolides/streptogramins vs penicillin antibiotics	Symptoms rated by participant or medical practitioner	Macrolides/streptogramins were superior	0.84 (0.73-0.97)	25	2488
Oral macrolide vs IV ^c penicillin	Symptoms rated by participant or medical practitioner	Oral therapy was superior	0.85 (0.73-0.98)	3	419
Penicillin vs cephalosporin	Symptoms rated by participant or medical practitioner	No difference in treatment effect	0.99 (0.68-1.43)	3	88
Cephalosporin vs cephalosporin ^d	Symptoms rated by participant or medical practitioner	No difference in treatment effect	1.00 (0.94-1.06)	6	538

^aPrimary outcomes included symptoms rated by participant or medical practitioner (eg, duration and intensity of fever, pain, redness of the affected area, swelling of the skin surface and subcutaneous tissue, blister formation), proportion symptom - free (*cure*), and at a time specified by the study authors), the proportion with severe complications (eg, severe sepsis, multi-organ failure, or death), and quality of life scores (ie, generic and disease-specific items and return to normal activity).

^bRR: relative risk.

^cIV: intravenous.

^dAggregate data from studies evaluating the following cephalosporins: ceftriaxone, cefdinir, cefonicid, cefditoren, cefadroxil, and cefuroxime.

The review reported insufficient data to determine the ideal duration of therapy. International recommendations for treatment duration in SSTIs are inconsistent (5-14 days) [2]—however, this is largely based on expert opinion, with few randomized

controlled trials evaluating this parameter. Future research should address this limitation to maximize patient benefit while reducing the effects of prolonged exposure.

Conflicts of Interest

RD is a Joint Coordinating Editor for *Cochrane Skin*, a dermatology section editor for *UpToDate*, a Social Media Editor for the *Journal of the American Academy of Dermatology* (JAAD), a Podcast Editor for the *Journal of Investigative Dermatology* (JID), Editor-in-Chief of *JMIR Dermatology*, and a coordinating editor representative on *Cochrane Council*. TS is an editorial board member-at-large for *JMIR Dermatology*.

Editorial Notice

The views expressed in this paper are those of the author(s) and in no way represent the Cochrane Library or Wiley.

This article is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2010, Issue 6, DOI: 10.1002/14651858.CD004299 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

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Abbreviations

SSTI: skin and soft tissue infection

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Research Letter

From the Cochrane Library: Interventions for Mycosis Fungoides

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mycosis fungoides; cutaneous T cell lymphoma; CTCL; psoralen plus ultraviolet-A; PUVA; systematic review; lymphoma; cancer; cancer treatment; cancer intervention; Alibert-Bazin syndrome

Mycosis fungoides (MF) is a chronic malignant condition characterized by a proliferation of clonal T helper cells in the skin. MF remains difficult to treat despite being the most common cutaneous T cell lymphoma. The disease is often refractory, with existing treatments providing only a short duration of clinical response [1]. A 2020 Cochrane review, “Interventions for mycosis fungoides,” provides a comprehensive review of evidence from 20 randomized clinical trials of local and systemic interventions for Alibert-Bazin-type MF (N=1369) [2]. Interventions evaluated in this review included topicals, intralesional therapies, phototherapy, total skin electron beam irradiation, radiotherapy, chemotherapy, extracorporeal photochemotherapy (ECP), biologics, and combination therapies.

The authors aimed to assess the efficacy and safety of interventions for MF using two primary outcome measures: health-related quality of life (HRQoL) and adverse events (AEs). Secondary outcomes included complete response (CR) and objective response rate (ORR). A CR was defined as the complete disappearance of all clinical evidence of disease. The ORR was defined as the proportion of patients with a CR or partial response, meaning the regression of measurable disease of at least 50% in the T, N, M, and B categories. Key outcomes

are reported in [Table 1](#). HRQoL was only reported in two studies that could not be analyzed together as it was divided by responder versus nonresponder rather than by treatment group. Common AEs ranged from mild symptoms to severe events. Overall, the evidence indicated that the more aggressive therapies (systemic chemotherapy and combination therapies) resulted in more severe AEs. From all therapies, the CR ranged from 0% to 83% (median 31%), and the ORR ranged from 0% to 88% (median 47%).

Data analysis of the five trials assessing the use of psoralen plus UV-A (PUVA) contributed to the key findings of this review, as it is first-line therapy for early-stage MF and is often used as adjunctive treatment in advanced stages. The authors found no evidence to support the addition of bexarotene or intralesional interferon- α (IFN- α) to PUVA when compared to PUVA alone. Separately, they noted that PUVA combined with IFN- α may lead to a higher CR when compared to IFN- α combined with acitretin. The authors did not find evidence to refute the recommendation of PUVA as a first-line treatment. There was insufficient evidence for adjunctive or alternative therapies such as acitretin or ECP to treat MF.

Using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria, the authors report a lack of high-certainty evidence to guide MF treatment. Many trials included in the review were either inadequate in methodological

quality, heterogenous in design, or had insufficient sample sizes. Reported outcomes varied across studies, prohibiting conclusive assessments of the safety, efficacy, and HRQoL impact of these interventions.

Table 1. Summary of key primary and secondary outcomes.

RCTs ^{a,b}	Patients, n	Comparison	Anticipated absolute effects (95% CI) ^c	Relative effect (95% CI)	Quality of evidence (GRADE ^d approach)
1	122	PUVA ^e vs IFN- α ^f + PUVA	<ul style="list-style-type: none"> • HRQoL^g: NM^h • AEsⁱ: NM • CR^j: 731 per 1000 vs 783 per 1000 (636-958) • ORR^k: NM 	<ul style="list-style-type: none"> • HRQoL: NM • AEs: NM • CR: RR^l 1.07 (0.87-1.31) (1) • ORR: NM 	<ul style="list-style-type: none"> • (1) Low
2	16	PUVA vs ECP ^m	<ul style="list-style-type: none"> • HRQoL: NM • AEs: Mild nausea after PUVA (n=NRⁿ), hypotension in ECP group (n=1) • CR: 250 per 1000 vs 50 per 1000 (3-903) • ORR: 750 per 1000 vs 53 per 1000 (0-750) 	<ul style="list-style-type: none"> • HRQoL: NM • AEs: NM • CR: RR 0.20 (0.01-3.61) (1) • ORR: RR 0.08 (0.01-1.17) (2) 	<ul style="list-style-type: none"> • (1) Very low • (2) Very low
3	93	PUVA vs PUVA + bexarotene	<ul style="list-style-type: none"> • HRQoL: NM • AEs: NM • CR: 222 per 1000 vs 313 per 1000 (158-622) • ORR: 489 per 1000 vs 460 per 1000 (298-704) 	<ul style="list-style-type: none"> • HRQoL: NM • AEs: photosensitivity RR 2.68 (0.11-64.04) (1) • CR: RR 1.41 (0.71-2.80) (2) • ORR: RR 0.94 (0.61-1.44) (3) 	<ul style="list-style-type: none"> • (1) Low • (2) Low • (3) Low
4	82	IFN- α + PUVA vs IFN- α + acitretin	<ul style="list-style-type: none"> • HRQoL: NM • AEs: flu-like symptoms 525 per 1000 vs 693 per 1000 (483-987) • CR: 700 per 1000 vs 378 per 1000 (245-588) • ORR: NM 	<ul style="list-style-type: none"> • HRQoL: NM • AEs: RR 1.32 (0.92-1.88) (1) • CR: RR 0.54 (0.35-0.84) (2) • ORR: NM 	<ul style="list-style-type: none"> • (1) Low • (2) Low
5	27	No maintenance vs PUVA maintenance	<ul style="list-style-type: none"> • HRQoL: NM • AEs: NE^o • CR: NE • ORR: NM 	<ul style="list-style-type: none"> • HRQoL: NM • AEs: NE • CR: NE • ORR: NM 	<ul style="list-style-type: none"> • NR

^aRCT: randomized controlled trial.

^bThe studies were ordered by summary findings numbers assigned in the original Cochrane review [2].

^cThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^dGRADE: Grading of Recommendations, Assessment, Development and Evaluations.

^ePUVA: psoralen plus UV-A.

^fIFN- α : interferon- α .

^gHRQoL: health-related quality of life.

^hNM: not measured.

ⁱAE: adverse event.

^jCR: complete response.

^kORR: objective response rate.

^lRR: risk ratio.

^mECP: extracorporeal photochemotherapy.

ⁿNR: not reported.

^oNE: not estimable based on reported data.

Although MF, particularly early stage, generally portends a favorable prognosis, a recent cause of death analysis combining

all stages of the disease revealed that patients with MF are most likely to die of the disease [3]. The incidence of MF has been

increasing over the past 50 years without concurrent improvement in evidence-based treatment options [3]. In line with most MF treatment guidelines, this review supports PUVA as a major intervention used in MF—a therapy that may be limited by a maximum lifetime dose after which increased risk

for melanoma and squamous cell carcinoma become a concern [4]. Thus, future efforts should be directed toward high-quality studies with patient-reported outcomes, safety, and efficacy of alternative MF interventions [5].

Editorial Notice

This article is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2020, Issue 7, DOI: 10.1002/14651858.CD008946.pub3 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

Conflicts of Interest

AHK does not have any conflicts of interest. RPD is a joint coordinating editor for *Cochrane Skin*, editor in chief of *JMIR Dermatology*, a dermatology section editor for *UpToDate*, a social media editor for the *Journal of the American Academy of Dermatology (JAAD)*, and a podcast editor for the *Journal of Investigative Dermatology (JID)*. He is also a coordinating editor representative on *Cochrane Council*. TES is an editorial board member-at-large for *JMIR Dermatology*. TW is a section editor for the *Journal of the German Society of Dermatology* and the *Journal of Evidence and Quality in Health Care*.

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Abbreviations

AE: adverse event

CR: complete response

ECP: extracorporeal photochemotherapy

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

HRQoL: health-related quality of life

IFN- α : interferon- α

JAAD: Journal of the American Academy of Dermatology

JID: Journal of Investigative Dermatology

MF: mycosis fungoides

ORR: objective response rate

PUVA: psoralen plus UV-A

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Original Paper

Improving Skin Color Diversity in Cancer Detection: Deep Learning Approach

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Abstract

Background: The lack of dark skin images in pathologic skin lesions in dermatology resources hinders the accurate diagnosis of skin lesions in people of color. Artificial intelligence applications have further disadvantaged people of color because those applications are mainly trained with light skin color images.

Objective: The aim of this study is to develop a deep learning approach that generates realistic images of darker skin colors to improve dermatology data diversity for various malignant and benign lesions.

Methods: We collected skin clinical images for common malignant and benign skin conditions from DermNet NZ, the International Skin Imaging Collaboration, and Dermatology Atlas. Two deep learning methods, style transfer (ST) and deep blending (DB), were utilized to generate images with darker skin colors using the lighter skin images. The generated images were evaluated quantitatively and qualitatively. Furthermore, a convolutional neural network (CNN) was trained using the generated images to assess the latter's effect on skin lesion classification accuracy.

Results: Image quality assessment showed that the ST method outperformed DB, as the former achieved a lower loss of realism score of 0.23 (95% CI 0.19-0.27) compared to 0.63 (95% CI 0.59-0.67) for the DB method. In addition, ST achieved a higher disease presentation with a similarity score of 0.44 (95% CI 0.40-0.49) compared to 0.17 (95% CI 0.14-0.21) for the DB method. The qualitative assessment completed on masked participants indicated that ST-generated images exhibited high realism, whereby 62.2% (1511/2430) of the votes for the generated images were classified as real. Eight dermatologists correctly diagnosed the lesions in the generated images with an average rate of 0.75 (360 correct diagnoses out of 480) for several malignant and benign lesions. Finally, the classification accuracy and the area under the curve (AUC) of the model when considering the generated images were 0.76 (95% CI 0.72-0.79) and 0.72 (95% CI 0.67-0.77), respectively, compared to the accuracy of 0.56 (95% CI 0.52-0.60) and AUC of 0.63 (95% CI 0.58-0.68) for the model without considering the generated images.

Conclusions: Deep learning approaches can generate realistic skin lesion images that improve the skin color diversity of dermatology atlases. The diversified image bank, utilized herein to train a CNN, demonstrates the potential of developing generalizable artificial intelligence skin cancer diagnosis applications.

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KEYWORDS

deep learning; neural network; machine learning; algorithm; artificial intelligence; skin tone diversity; data augmentation; skin cancer diagnosis; generalizability; skin; cancer; diagnosis; diagnostic; imaging; dermatology; digital health; image generation; generated image; computer-generated; lesion

Introduction

The “white lens” phenomenon has led to the underrepresentation of dark skin pathology images in dermatology resources [1]. A recent analysis of several dermatology textbooks utilized to educate dermatologists showed that dark skin images represent merely 4% to 18% of the total number of images [2]. As a result, it is challenging for dermatologists to properly diagnose and treat skin pathology in people of color.

Applications utilizing artificial intelligence (AI) have been developing at a rapid pace to aid clinicians in making diagnoses [3,4]. Deep learning (DL), a branch of AI, has been widely employed to develop models as accurate as specialist dermatologists in diagnosing skin cancer [5-8] and common skin conditions [9-12]. However, a major drawback facing the mainstream adoption of DL applications in dermatology is the paucity of training data diversity leading to nonrobust models [13,14].

Han et al [15] developed a DL model to diagnose malignant and benign skin lesions using clinical images. According to their results, the performance of the model was highly dependent on the diversity of the training data. Thus, DL models trained on data with a certain skin color range could not be generalized when tested on data collected from a different population [16]. Rahman et al [17] utilized International Skin Imaging Collaboration (ISIC) images to train and test 5 DL models to diagnose various malignant and benign skin lesions [18]. The models achieved a recall of 88%, 89%, 91%, 88%, and 84%, respectively, and the performance was further boosted by developing an ensemble of the implemented models that achieved a recall of 94%. ISIC images were also utilized to develop a DL framework, DermoExpert [19], to classify up to 7 malignant and benign skin lesions. The framework was trained and tested on ISIC-2016, ISIC-2017, and ISIC-2018 images and achieved an AUC of 0.96, 0.95, and 0.97 for the 3 data sets, respectively.

Although ISIC provides a large publicly available skin images archive, the images were mainly collected from the United States, Europe, and Australia [13], where light skin colors are dominant. This was also confirmed by Kinyanjui et al [20], who studied the skin tone distribution of ISIC images and showed that the skin tone of the images primarily ranged from very light to intermediate. Thus, the aforementioned models trained and tested on ISIC images are not expected to be generalizable to darker skin colors.

Motivated by this necessity, we proposed an algorithm development and validation protocol to perform skin cancer early detection for all skin colors [21]. In the protocol, we considered clinical images to develop the model because clinical images are easy to obtain, unlike dermoscopic images that require a specialist and microscopy. In this paper, we discuss the development and initial internal validation of skin image generation for underrepresented skin colors in publicly available data sets (Phases 2 and 3 of the protocol). This paper aims to (1) generate realistic images with malignant and benign skin lesions using 2 deep learning methods, (2) extensively evaluate the generated images using quantitative ratings as well as

qualitative human expert and nonexpert ratings, and (3) develop a preliminary classifier, trained with the generated images, to categorize the images as malignant or benign and to study the generated images' effect on the classification accuracy.

The remaining article is organized as follows: the methods section explains the materials and techniques utilized to generate and evaluate the images. The subsequent section shows the experimental results of all components involved in this work, and the final section highlights our work limitations, discusses the proposed work in comparison with other existing studies, and concludes our work.

Methods

Background

In this work, we implement 2 phases of our ongoing study that aims at leveraging deep learning to improve skin color diversity and thus malignancy detection in any skin color using clinical images. The first phase of our study [21] focused on quantifying the underrepresentation of darker skin colors in dermatology atlases by developing a skin tone categorization tool. The second and third phases of the study, implemented herein, aim to generate images with darker skin color, extensively assess the generated images using several evaluation metrics, and study the impact of the generated images on malignancy detection by developing a classification model trained on the generated images. Finally, the fourth phase, expected to be completed by the end of 2022, will focus on developing an accurate malignancy detection classification model. This model will compile the generated images with text descriptions of skin cancer clinical presentations in darker skin colors and use novel deep learning architectures and ensemble learning approaches to improve classification accuracy. In this section, we explain the characteristics of the utilized data, the image generation methods, and the evaluation techniques employed to achieve the objectives of Phases 2 and 3.

Study Data Set

We collected 1701 clinical images representing several malignant and benign skin lesions from the publicly available skin image repositories DermNet NZ (994 images) [22], ISIC-2018 JID editorial images (100 images) [17], and Dermatology Atlas (607 images) [23]. Images from DermNet NZ and ISIC (1094 images), referred to as set A, were utilized for generating images, training, and validating the classifier. Meanwhile, Dermatology Atlas images (607 images), referred to as set B, were utilized to test the classifier. The distribution of the data as malignant and benign is listed in Table 1.

The skin tone diversity of the study data sets was investigated using our skin tone categorization tool [21]. The results, summarized in Table 2, showed that the majority (84.1%, n=920) of set A images were categorized as light and intermediate skin tones, while set B was more diverse and had varying skin tone distributions. Based on this, set B will facilitate our evaluation of the generalizability of the classification model developed using the generated images, as it has variant skin tone distribution compared to the training data.

Table 1. Study data sets for malignant and benign class distribution [21]. Set A (n=1094): training and validation set; set B (n=607): testing set.

Tumor type	Set A, n (%)	Set B, n (%)
Malignant	634 (58)	508 (83.7)
Benign	460 (42)	99 (16.3)

Table 2. Skin tone distribution of the study data sets. Set A (n=1094): training and validation set; set B (n=607): testing set.

Skin tone	Set A, n (%)	Set B, n (%)
Light	690 (63.1)	133 (21.9)
Intermediate	230 (21.0)	198 (32.6)
Tan	110 (10.1)	131 (21.6)
Brown	62 (5.7)	134 (22.1)
Black	2 (0.18)	11 (1.8)

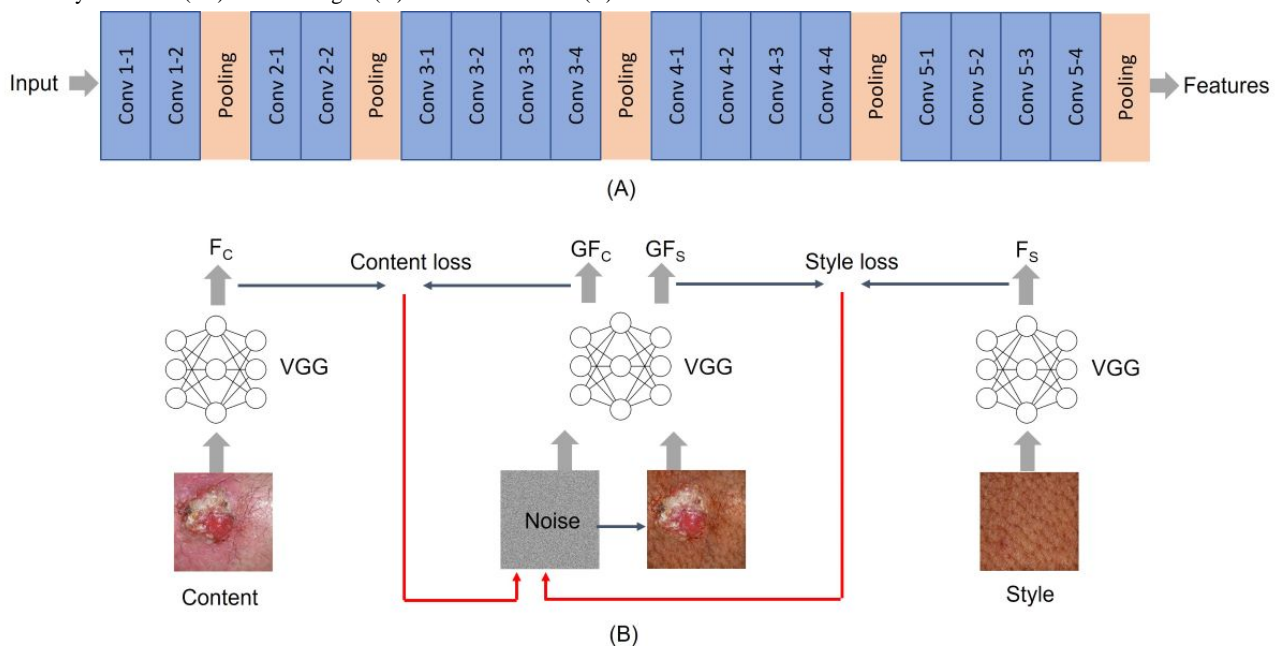
Image Generation

Style Transfer

Style transfer (ST) [24] is an image generation technique developed based on the visual geometry group (VGG)-19 network architecture and trained on the ImageNet database with millions of images [25]. ST utilizes 16 convolutional layers (Conv), 5 average pooling, and no fully connected layers of the VGG-19 architecture, as illustrated in Figure 1A. The ST method, as demonstrated in Figure 1B, primarily works by extracting features from content and style images denoted as F_C and F_S . Then, it iteratively blends the features to generate a new image with content and style features (GF_C , GF_S). The content and style losses are calculated as the difference between the original (F_C , GF_C) and the generated features (F_S , GF_S). The

total loss is backpropagated to the VGG network to improve the quality of the generated image.

Since convolutional neural networks (CNNs) trained with an adequate number of annotated data on object recognition can extract high-level features from images independent of their content [26], the ST method can be generalized for feature extraction from skin lesion images. Therefore, ST can be utilized to generate darker skin images without retraining the VGG network. ST was utilized in this work by extracting the features of a light skin image containing the skin pathology and a style image with the target skin color. A new image containing an optimized blend of both feature sets was subsequently generated, starting from a noise image and iteratively improving by minimizing the total loss, as illustrated in Figure 1B. The fine-tuning details of the ST method are discussed in Multimedia Appendix 1.

Figure 1. Style transfer (ST) in skin images. (A) VGG architecture. (B) Process of ST.

Deep Blending

Deep blending (DB) is an integration of ST and Poisson image blending methods [27], wherein the object of interest from a content image is transferred to the style image while minimizing the sharp intensity and texture change between the content and style images [28]. As in ST, DB utilizes the VGG network to extract the features of the input images and iteratively updates the output image using the calculated loss functions. However, DB works only on the object of interest from the content image and thus requires a segmented object. Moreover, DB essentially works on the blending region where the content object meets the style image. Therefore, DB utilizes 3 loss functions: (1) Poisson-based gradient loss to minimize the change of the blending region gradient, (2) content loss to ensure the semantic of the blending region is similar to the content object, and (3) style loss to ensure the texture of the blending region is similar to the style image. Finally, DB performs 2 rounds of blending; the first round employs the content object and the style image, and the second employs the output blended image of the first

Figure 2. Skin tone classification. ITA: individual typology angle.

Skin Classification	Tan	Brown	Black
			
ITA	11	-7.7	-63.2

Evaluation

Quantitative Evaluation

The quantitative evaluation was performed using the blind referenceless image spatial quality evaluator (BRISQUE) and the structural similarity index measure (SSIM) to assess realism and disease presentation, respectively. BRISQUE is a referenceless metric that quantifies the loss of image realism in the presence of distortions solely using the image being assessed [32]. This method assigns a quality score to each image that correlates well with human quality judgment [32]. The BRISQUE evaluation method is based on 2 main concepts: (1) real images maintain regular statistical properties, and (2) normalized brightness coefficients of a real image approximately follow a Gaussian distribution. As such, image distortion can be captured by a change in the expected statistical properties or deviation from a Gaussian distribution (such as the generalized Gaussian distribution [33] and the asymmetric generalized Gaussian distribution [34], as explained in [Multimedia Appendix 3](#)).

The second metric, SSIM, compares the structure, texture, and edges of a reference image with a modified image and provides a similarity score [35]. SSIM was previously used to evaluate the quality of the generated skin lesion images [36]; therefore, SSIM is employed in this study to evaluate the similarity of the

round and the style image. The fine-tuning details of the DB method are discussed in [Multimedia Appendix 1](#).

Target Skin Color Selection

The target skin color is the style needed to synthesize images in ST and DB methods. To generate images for the underrepresented skin colors in set A, tan, brown, and black skin colors were selected. The selection of the target style images was determined using the individual typology angle (ITA) calculated from the input transformed images [29]. Consequently, the angle was mapped to a skin class according to predefined ITA ranges [30]. The ITA calculation and mapping are explained in [Multimedia Appendix 2](#).

Figure 2 shows the selected skin images, to be utilized as style images, with the ITA score and skin classification. The tan skin image was obtained from Dermatology Atlas [23], while the brown and dark skin images were obtained from Shutterstock [31] through a standard license.

generated images with the content image including the disease to measure disease presentation. The SSIM calculation is explained in [Multimedia Appendix 3](#).

Qualitative Evaluation

For the qualitative assessment, 62 individuals with varying backgrounds participated in evaluating the generated images. Of the 62 participating individuals, 41 (66.1%) had no medical background and 21 (33.9%) were medical personnel that included 10 (47.6%) attending physicians, 2 (9.5%) physicians in training, 1 (4.8%) nurse, and 8 (38.1%) dermatologists. The first task was a human visual Turing test (VTT), wherein participants (with and without a medical background) were asked to classify the images as real or generated. The responses of the VTT were analyzed to (1) determine the significance of background (medical versus nonmedical personnel) and experience in discovering the generated images and (2) estimate the quality of the generated images by calculating the classification accuracy, false positive rate (FPR), defined as the ratio of generated images classified as real, and true positive rate (TPR), defined as the ratio of real images classified as real.

The second task was a disease identification test carried out solely by dermatologists with varying experience levels. The responses to this test were analyzed to measure the recall (ratio of correctly diagnosed images by dermatologists) of the real

and generated images. The 95% CI was calculated using the Clopper-Pearson method [37] to estimate the uncertainty of the reported results.

Preliminary Classification Evaluation

To study the effect of the generated images on skin color diversity, the generated images were used to augment the original images of set A to train a CNN and classify the image as malignant or benign. The 1094 images of set A were randomly split, with 80% (n=875) used for training the network and 20% (n=219) used for validation. The CNN training followed 4 data utilization approaches, as illustrated in Figure 3: (a) use the images directly for training without performing any augmentation; (b) augment the images with their corresponding generated tan, brown, and black images; (c) augment the images through geometric transformations, such as flipping, rotating, and adding noise [38]; and (d) augment the images with the generated and transformed images. All models were validated on the same validation set (219 images)

and evaluated using separate test data, set B, which included 607 real images with diverse skin tone distribution, as illustrated in Table 2.

ResNet-50 [39] pretrained on ImageNet images was utilized in our work due to its applicability to dermatology diagnostic tasks [40,41]. The ResNet-50 architecture consists of the 5 stages shown in Figure 4A. For skin lesion classification, we customized ResNet-50 by adding an average pooling layer, a fully connected layer, and SoftMax to classify the lesions as malignant or benign, as shown in Figure 4B. Transfer learning was applied when training the ResNet-50, wherein we froze the first 4 blocks of the ResNet-50 to make use of the ImageNet’s gained weights and trained the last block with the newly added layers to gain new weights. The customized ResNet-50 was trained for 30 epochs and optimized using an Adam optimizer [42] with a learning rate of 0.001. The learning rate was incrementally reduced when there was no improvement in the validation accuracy for 5 consecutive epochs to allow the models to learn more optimal weights [43].

Figure 3. Image classification process. CNN: convolutional neural network; Tr: training set; Ts: test set; VI: validation set.

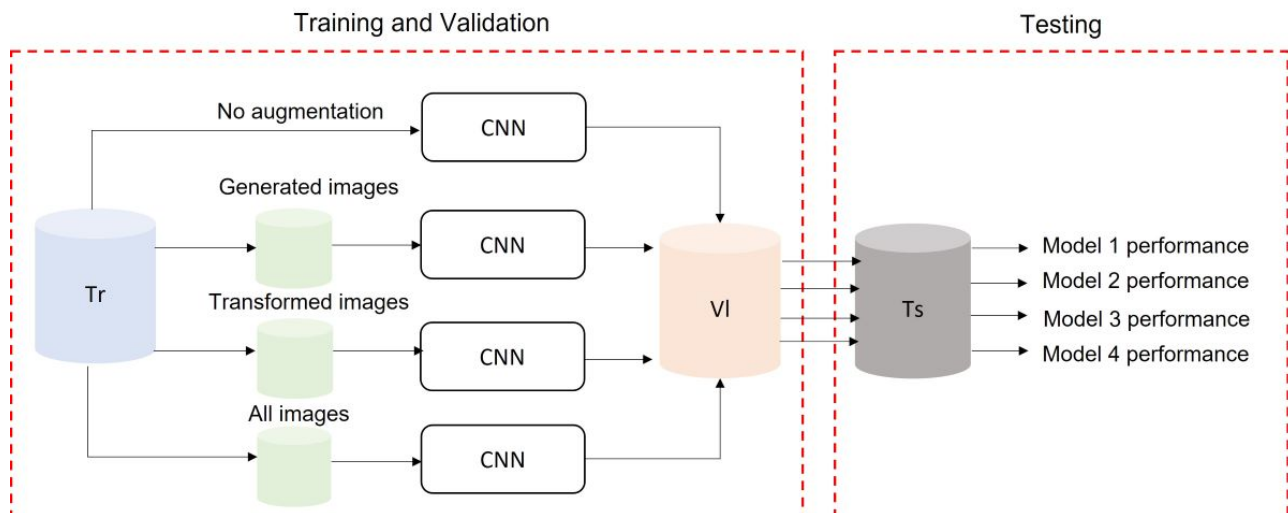
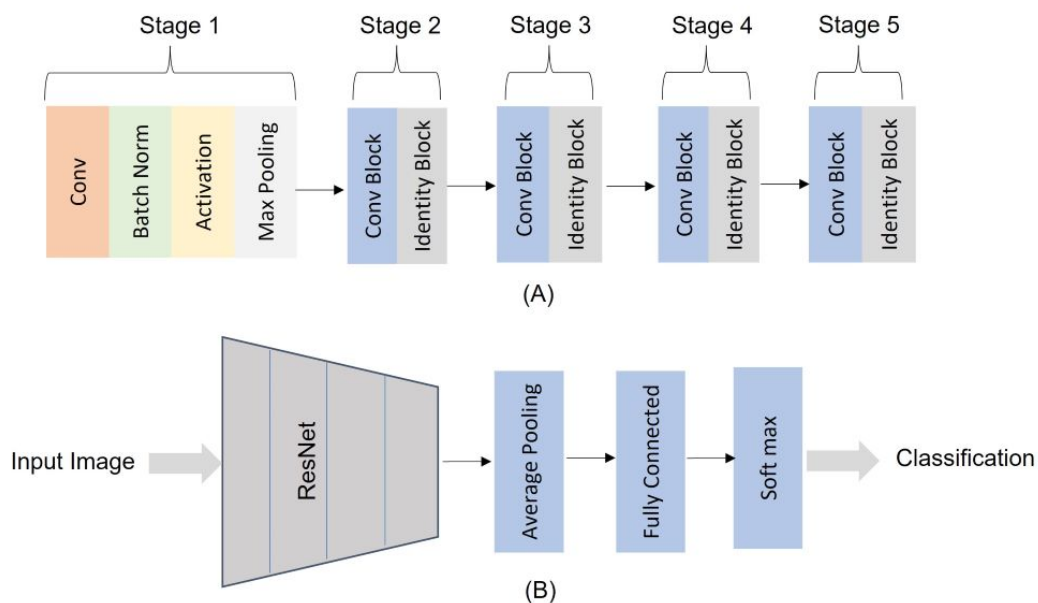


Figure 4. Classification network. (A) ResNet-50 architecture and (B) the customized ResNet-50.



Ethics Approval

All images utilized in our work were collected from publicly available deidentified data sets. Therefore, we do not require ethics approval.

Results

Implementation Details

All the developed models were implemented on Google Collaboratory Pro with a NVIDIA Tesla P100 GPU. We used Keras [44] with Tensorflow [45] to develop and optimize the models. The average time to generate a single image using the ST method was 46 seconds and 9 minutes using the DB method (performing 2 rounds of image optimization). The time for training the classification models varied based on the data utilization approach; the average training time was 14, 34, 34, and 47 minutes for the no augmentation, generated image augmentation, transformed image augmentation, and all images augmentation, respectively (Figure 3).

Quantitative Evaluation

Based on the skin tone analysis of the study data set, the 920 images categorized as light (690) and intermediate (230) skin colors were utilized as content, and 2760 images were generated using each method for the tan, brown, and dark style images. Tables 3 and 4 report the average normalized BRISQUE and average SSIM scores for each skin color using ST and DB generation methods, respectively. As the BRISQUE measured

the loss of realism in the generated images, lower BRISQUE scores indicated higher realism. As the SSIM measured the similarity between the generated images and the content images, higher SSIM scores indicated a higher similarity to the image including the disease.

It can be seen that the ST method outperformed the DB method in terms of realism by achieving significantly lower average BRISQUE scores in all skin tones (Table 3). The overall BRISQUE score of the ST method was 0.23 (95% CI 0.19-0.27) compared to the DB score of 0.63 (95% CI 0.59-0.67). In terms of disease presentation, ST achieved higher average SSIM scores in all skin tones (Table 4). The overall SSIM score of the ST method was 0.44 (95% CI 0.40-0.49) compared to 0.17 (95% CI 0.14-0.21) for the DB method. Across the different tones, there was a consistent change in the BRISQUE metric for both methods resulting from the quality variation of the utilized style images. Similarly, the SSIM changed across skin colors, decreasing for ST and DB for darker colors due to the deviation from the light skin color of the content images.

A visual qualitative comparison between the images generated by the ST and DB methods with respect to the real images is demonstrated in Figure 5. The ST-generated images showed clear disease presentation while adding up the pigmentation on the lesion region to match the darker skin color. However, the DB-generated images included the disease region from the content image and focused only on blending the border of the disease with the style image. Therefore, the ST-generated images looked more realistic compared to the DB-generated images.

Table 3. Average normalized blind referenceless image spatial quality evaluator (BRISQUE) scores of the style transfer (ST) and deep blending (DB) methods.

Method	Tan	Brown	Black
ST ^a	0.13 (95% CI 0.08-0.19)	0.35 (95% CI 0.27-0.42)	0.22 (95% CI 0.15-0.29)
DB ^b	0.55 (95% CI 0.47-0.63)	0.93 (95% CI 0.89-0.97)	0.42 (95% CI 0.34-0.49)

^aST: style transfer.

^bDB: deep blending.

Table 4. Average structural similarity index measure (SSIM) scores of the style transfer (ST) and deep blending (DB) methods.

Method	Tan	Brown	Black
ST ^a	0.51 (95% CI 0.43-0.59)	0.44 (95% CI 0.36-0.52)	0.37 (95% CI 0.30-0.45)
DB ^b	0.20 (95% CI 0.14-0.26)	0.17 (95% CI 0.11-0.23)	0.15 (95% CI 0.09-0.21)

^aST: style transfer.

^bDB: deep blending.

Figure 5. Generated images using style transfer (ST) and deep blending (DB) compared to the real images.



Qualitative Evaluation

For the human qualitative evaluation component, we conducted 2 assessments, a VTT to evaluate the realism of the generated images and a disease identification assessment to evaluate disease presentation. As the ST method showed superior quantitative evaluation compared to DB, we conducted all human evaluations on the ST images.

The human VTT was performed on 45 real and 45 generated images to evaluate realism. A total of 54 participants, including 41 (75.9%) without a medical background and 13 (24.1%) medical personnel, including 10 (76.9%) attending physicians, 2 (15.4%) physicians in training, and 1 (7.7%) nurse, were asked to classify the images either as real or generated. First, we analyzed the scores of each participant to study the significance of the background and years of experience in identifying the generated images correctly. The generated score (number of generated images correctly identified) was set as the outcome, and the real score (number of real images correctly identified), background (medical versus nonmedical personnel), and years of experience (0: nonmedical personnel, 1: medical personnel with 2 to 5 years of experience, 2: medical personnel with 6 to 10 years of experience, and 3: medical personnel with more than 10 years of experience) were predictors.

Linear regression was utilized to investigate the significance of the predictors on the outcome. First, the generated score was modeled using the background only, which turned out to be insignificant ($P=.96$). Consequently, the generated score was modeled using the background and years of experience, which also showed no significance ($P=.65$ and $.61$, respectively). Finally, the real score was integrated as a predictor, and background and experience were not shown to be significant factors, ($P=.45$ and $.65$, respectively); however, the real score was significant ($P<.001$). The generated score in relation to the real score and the final fitted regression model is illustrated in Figure 6.

Consequently, we calculated the classification accuracy, FPR, and TPR to compare the generated images with the real ones. As illustrated in Figure 7, for all participating individuals regardless of background, the FPR was 0.62 (1511/2430 votes;

95% CI 0.60-0.64), and the TPR was 0.60 (1449/2430 votes; 95% CI 0.58-0.62), indicating high realism of the generated images. Moreover, there was no significant difference between the FPR of medical personnel and nonmedical personnel, which was 0.615 (95% CI 0.58-0.65) versus 0.624 (95% CI 0.60-0.65). The overall accuracy was 0.49 (95% CI 0.47-0.50), indicating that the participants had poor differentiation between generated and real images.

The second human qualitative assessment aimed to evaluate the accuracy of disease presentation in the generated images. We included a total of 80 images: 20 real images and 60 ST method-generated images (20 each for tan, brown, and black skin colors). The diseases included are shown in Figure 8. Eight expert dermatologists, masked to our study methodology and image sources, participated in a survey comprising real and generated images and chose a diagnosis most consistent with the image presented. The average recall (rate of correctly diagnosed lesions by dermatologists) of the real images was 0.76 (121 correct diagnoses out of 160) compared to 0.75 (360 correct diagnoses out of 480) for the generated images. Details of the recall for each disease group, image type, and skin color are demonstrated in Figure 8.

In Figure 8, the average recall of the generated images grouped by skin color, tan (G-Tan), brown (G-Brown), and dark (G-Dark), is represented by a red dot to compare to the real images. As this figure shows, basal cell carcinoma had the lowest average recall of the generated images compared to the real recall. In basal cell carcinoma, the tan-generated images had a recall of 0.81 compared to a real image recall of 0.69; however, the brown and dark images had a significantly lower recall of 0.44 and 0.38, respectively. Therefore, further analysis was performed to gain a deeper insight into the disease misdiagnosis.

The results of the recall experiment were summarized as confusion matrices for the real, generated tan, brown, and dark images, as shown in Figure 9A-D. The diagonal of the confusion matrix represents the rates of correctly diagnosed diseases (true positives), while all other numbers in the matrix represented the misdiagnosis rates.

It can be observed that basal cell carcinoma in the brown and dark skin images was mainly misdiagnosed as melanoma with a misidentification rate of 0.31 and 0.62, respectively. A closer look at the confusion matrix of the dark generated images (Figure 9D) reveals that intraepidermal carcinoma was also misdiagnosed as melanoma with a misidentification rate of 0.25.

In addition, halo nevus was misidentified as melanoma with a rate of 0.19. On the other hand, melanoma was best identified in the dark skin color with a rate of 0.94. This high rate could be explained by the misdiagnosis of several lesions as melanoma. Thus, any pigmented lesion on the dark skin was primarily misdiagnosed as melanoma.

Figure 6. Generated score versus the real score. Line represents the linear regression model with the standard error shaded.

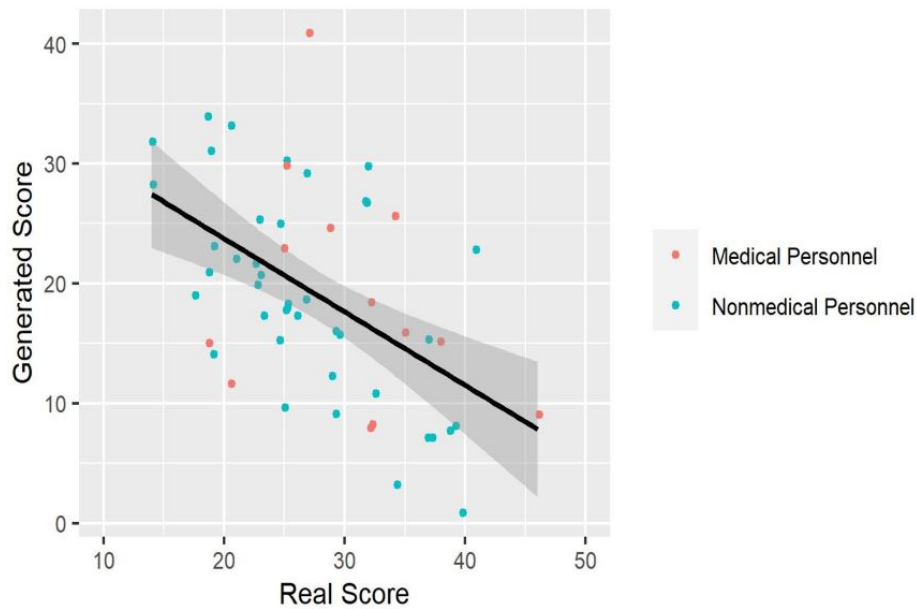


Figure 7. Evaluation of the human Visual Turing test results, with error bars representing 95% CI. FPR: false positive rate; TPR: true positive rate.

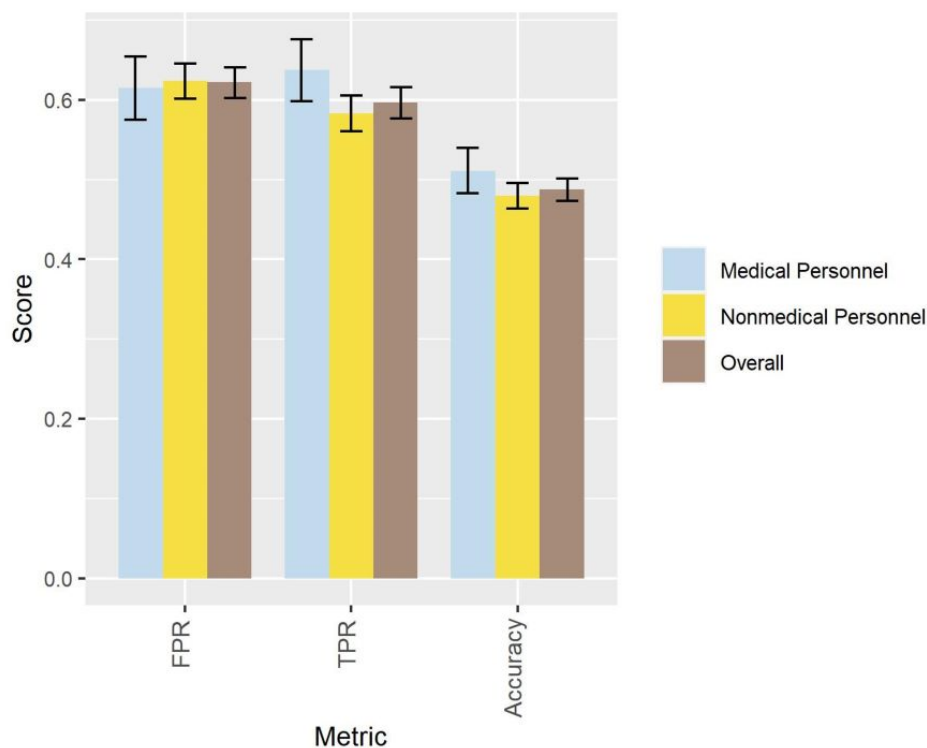


Figure 8. Recall of the utilized diseases, with error bars representing 95% CI. AK: actinic keratosis; AN: atypical nevi; BCC: basal cell carcinoma; IEC: intraepidermal carcinoma; HN: halo nevus; Hem: hemangioma; Mel: melanoma; SCC: squamous cell carcinoma; SK: seborrheic keratosis; VM: vascular malformation.

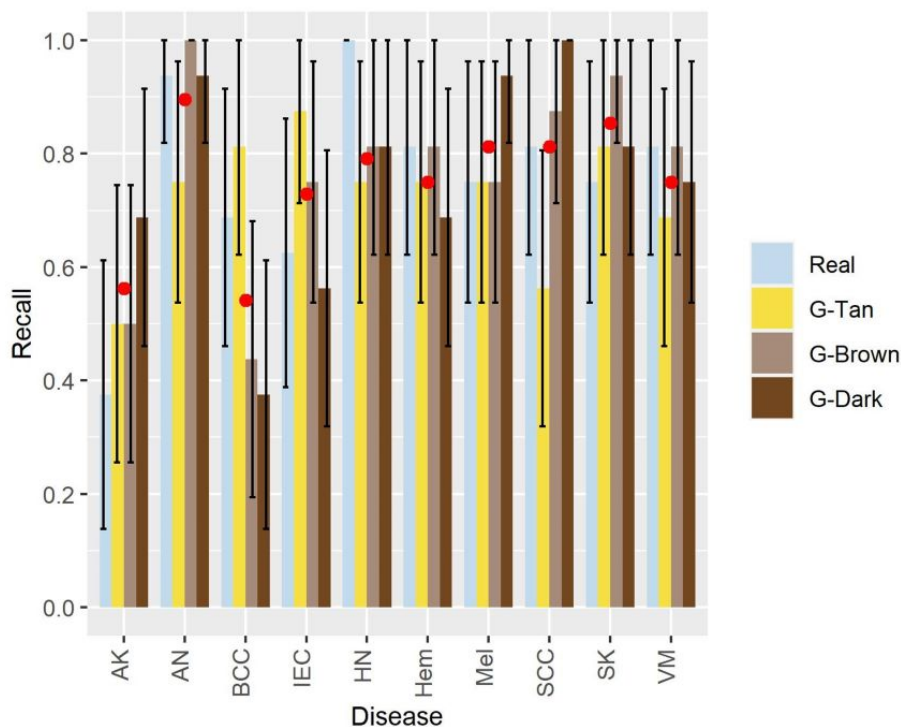
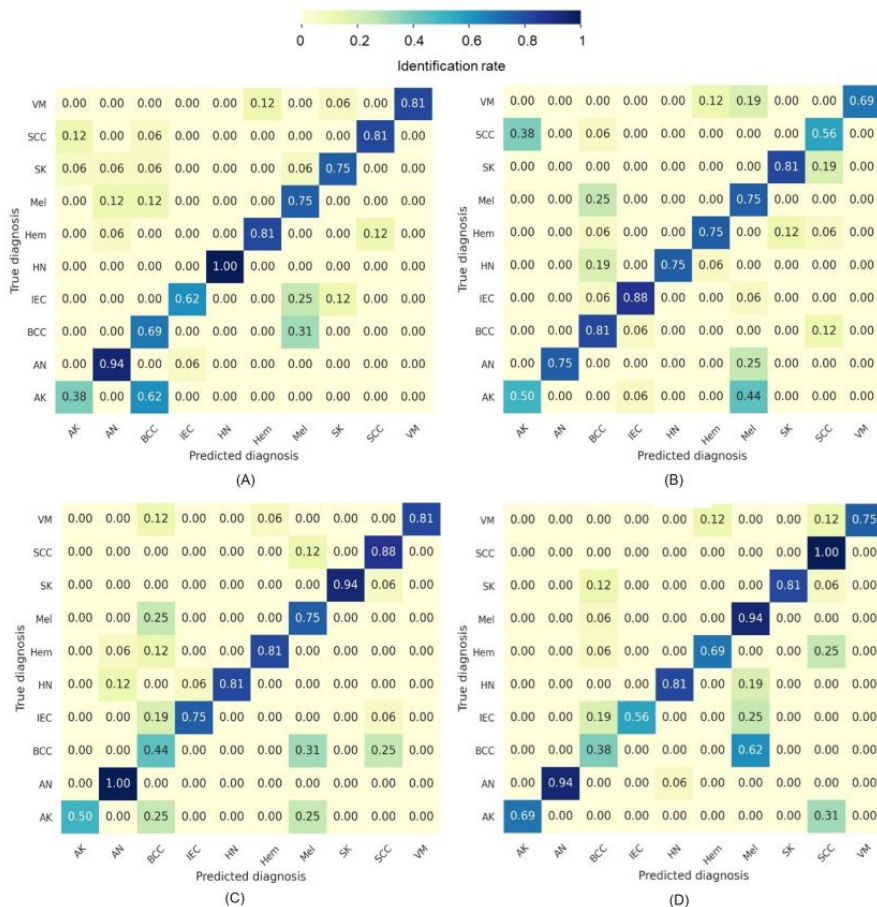


Figure 9. Confusion matrix of the real and generated images. (A) real images, (B) tan-generated images, (C) brown-generated images, and (D) dark-generated images.



Preliminary Classification Evaluation

A total of 4 models were developed: trained on set A images without augmentation (model 1), trained on set A augmented with the ST-generated images (model 2), trained on set A augmented with geometric transformations (eg, flipping, rotation, and noise) (model 3), and set A augmented with both the generated and transformed images (model 4). To assess the models' generalizability, all were tested on set B, which entirely consisted of real images and was characterized by a different skin color distribution compared to the training set A (Table 2).

A comparison between the accuracy and AUC of the developed models is shown in Table 5. It can be observed that model 1 is the least performing model because it has the least discrimination ability characterized by the least AUC of 0.63. On the other hand, model 2 is the best performing model with an accuracy and AUC of 0.76 and 0.72, respectively, indicating the significant impact of the skin color augmentation on the model's generalizability. With respect to model 3 (AUC 0.66), a comparable performance to model 1 (AUC 0.63) can be noticed, indicating that geometric transformations did not significantly increase the model's performance. Finally, model

4 (AUC 0.69) showed improved performance compared to model 3 (AUC 0.66) but decreased performance compared to model 2 (AUC 0.72), emphasizing that combining several data augmentations did not benefit the model.

It can be concluded that augmenting the data with diverse skin color images allowed the model to learn skin tone-related features; thus, model 2 was robust to the variations of the skin color in the test set. On the other hand, the geometric transformations did not provide the model with the variability needed to handle the deviation in skin tone distribution present in the test set. Therefore, when combined with the generated images, a decrease in performance was noticed, highlighting the importance of selecting consistent image augmentations that work to fill the gap between the training and testing data [38].

Finally, to evaluate the significance of the difference in the AUC between the best performing model (model 2) and all other models, the DeLong test to compare 2 ROC curves [46] was carried out. The difference in AUC between models 2 and 1 and between models 2 and 3 was significant ($P < .001$ and $P = .03$, respectively), while there was no significant difference in the AUC between models 2 and 4 ($P = .35$).

Table 5. Performance of the classification models on set B.

Models	Accuracy	AUC ^a
Model 1	0.56 (95% CI 0.52-0.60)	0.63 (95% CI 0.58-0.68)
Model 2	0.76 (95% CI 0.72-0.79)	0.72 (95% CI 0.67-0.77)
Model 3	0.56 (95% CI 0.52-0.60)	0.66 (95% CI 0.62-0.71)
Model 4	0.60 (95% CI 0.56-0.64)	0.69 (95% CI 0.65-0.74)

^aAUC: area under the curve.

Discussion

Principal Results

In this work, we proposed a DL-based approach to generate realistic skin images for underrepresented skin colors using publicly available white skin clinical images. We utilized the pathology of light skin images and healthy dark skin images to extract and blend disease and pigmentation features. The employed strategy of generating darker images based on feature blending helped to overcome the lack of dark skin images, as the utilized image generation techniques herein were trained to extract high-level features from images independently from their content [26]. In terms of evaluating the quality of the generated images, comprehensive qualitative and quantitative approaches were developed. Given that the qualitative analyses can be affected by the paucity of darker skin images and because human judgment (especially the disease diagnoses test) might vary based on skin color, we performed statistical and mathematical quantitative analyses to address this issue. The results emphasized that ST-generated images had high realism and disease presentation, characterized by a lower loss of realism and higher structural similarity scores for all skin colors compared to those based on the DB method. Moreover, the generated images achieved high FPR and disease recall when compared to the real images. Finally, the generated images contributed to improvement in the classification performance

when used to augment the training of ResNet-50 in comparison to other augmentation strategies.

Limitations

Our work has several noteworthy limitations and areas for future improvement. Lesion pigmentation is not the only factor that characterizes skin cancer in people of color; thus, other disease morphological features need to be integrated into our models. As such, in Phase 4, text features representing skin cancer clinical presentation on darker skin will be created based on the published literature and consequently utilized along with the augmented images to train the classification models. In addition, the classification accuracy that has been investigated herein needs to be improved; therefore, in Phase 4, several CCN architectures and ensemble learning methods will be implemented to boost the classification accuracy. Moreover, images with real pathology in people of color are required to improve model training and validation. Finally, it is worth mentioning that other novel skin tone scales have been recently developed, such as Google's Monk scale [47]. Thus, our skin tone categorization tool can benefit from investigating and validating such new scales.

Comparison With Prior Work

Image generation using DL has been applied in the literature to improve data balance. The generative adversarial network

(GAN) has been utilized to generate synthetic images for several malignant and benign lesions to overcome class imbalance [48]. The model was trained on 10,000 dermoscopic images from the ISIC-2018 data set, and the generated images were evaluated for realism by humans. A total of 3 dermatologists and 5 DL experts classified a random sample of the real and generated images as real or fake. The analysis showed that the human classification accuracy was around 50%, meaning that the raters were not able to clearly distinguish between real and generated images. However, generating images with various skin colors was not considered in the aforementioned study.

GAN was also employed to generate dermoscopic images to mitigate data imbalance. Three GAN models were trained on 2000 dermoscopic images from the ISIC-2017 data set [49]. To evaluate the generated images, the authors compared the normalized color histogram of the generated images with the training images. Their results showed a high similarity in the distribution of both real and generated images. Despite the high quality of the generated images, there was no focus on skin color.

In another study [50], the authors utilized GAN to generate clinical skin images for various skin conditions, in which the required input features (eg, skin color and lesion location) were manually encoded. Encoding of input features was required during all model development phases (eg, training, validation, and testing); thus, the developed model could not be deployed without feature encoding. Although the images could be generated with different skin colors using the encoding maps, no images were generated with dark skin colors.

In terms of evaluation, the realism of the generated images in the aforementioned study [50] was evaluated by conducting a

VTT with 10 participants, and the generated images had an average FPR of 0.3. Meanwhile, in our work, the VTT was conducted with 54 participants and achieved a higher FPR of 0.62. Moreover, the disease recall evaluation was conducted with 2 dermatologists and achieved an average recall of 0.45. However, in our work, the disease recall was assessed with 8 dermatologists and achieved a significantly higher average recall of 0.75. Furthermore, we performed a misdiagnosis analysis, and our findings strongly agreed with the published literature on skin cancer misdiagnosis in people of color [51].

Conclusion

Despite the recent advances of AI in dermatology diagnosis, the lack of skin color diversity when training AI models is a major pitfall. Until a sufficient real-world diverse image repository is collected, augmenting real images with generated darker skin images is the first step to implementing robust diagnosis models. The generated images in this work achieved high realism and disease recall scores when compared to the real images. In addition, the generated images augmented the publicly available white skin images, and a classification model was developed that outperformed the model trained without the generated images. In our future work, which will comprise Phase 4 of this study, we will focus on overcoming our previously mentioned limitations to boost the accuracy and robustness of the preliminary classification model discussed herein. After completing all study phases and addressing all discussed limitations, the resulting model will be a tool to aid general practitioners in diagnosing possible skin malignancy and thereby improve the efficiency and reduce the redundancy of referrals that expert dermatologists receive for further clinical assessments and biopsies.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Image generation fine-tuning.

[\[PDF File \(Adobe PDF File\), 516 KB - derma_v5i3e39143_app1.pdf\]](#)

Multimedia Appendix 2

Individual typology angle.

[\[PDF File \(Adobe PDF File\), 172 KB - derma_v5i3e39143_app2.pdf\]](#)

Multimedia Appendix 3

Quantitative evaluation details.

[\[PDF File \(Adobe PDF File\), 227 KB - derma_v5i3e39143_app3.pdf\]](#)

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Abbreviations

AI: artificial intelligence

AUC: area under the curve

BRISQUE: blind referenceless image spatial quality evaluator

CNN: convolutional neural network

DB: deep blending

DL: deep learning

FPR: false positive rate

GAN: generative adversarial network

ISIC: International Skin Imaging Collaboration

ITA: individual typology angle

NSERC: Natural Sciences and Engineering Research Council of Canada

SSIM: structural similarity index measure

ST: style transfer

TPR: true positive rate

VGG: visual geometry group

VTT: visual Turing test

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Original Paper

Assessing the Generalizability of Deep Learning Models Trained on Standardized and Nonstandardized Images and Their Performance Against Teledermatologists: Retrospective Comparative Study

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Abstract

Background: Convolutional neural networks (CNNs) are a type of artificial intelligence that shows promise as a diagnostic aid for skin cancer. However, the majority are trained using retrospective image data sets with varying image capture standardization.

Objective: The aim of our study was to use CNN models with the same architecture—trained on image sets acquired with either the same image capture device and technique (standardized) or with varied devices and capture techniques (nonstandardized)—and test variability in performance when classifying skin cancer images in different populations.

Methods: In all, 3 CNNs with the same architecture were trained. CNN nonstandardized (CNN-NS) was trained on 25,331 images taken from the International Skin Imaging Collaboration (ISIC) using different image capture devices. CNN standardized (CNN-S) was trained on 177,475 MoleMap images taken with the same capture device, and CNN standardized number 2 (CNN-S2) was trained on a subset of 25,331 standardized MoleMap images (matched for number and classes of training images to CNN-NS). These 3 models were then tested on 3 external test sets: 569 Danish images, the publicly available ISIC 2020 data set consisting of 33,126 images, and The University of Queensland (UQ) data set of 422 images. Primary outcome measures were sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC). Teledermatology assessments available for the Danish data set were used to determine model performance compared to teledermatologists.

Results: When tested on the 569 Danish images, CNN-S achieved an AUROC of 0.861 (95% CI 0.830-0.889) and CNN-S2 achieved an AUROC of 0.831 (95% CI 0.798-0.861; standardized models), with both outperforming CNN-NS (nonstandardized model; $P=.001$ and $P=.009$, respectively), which achieved an AUROC of 0.759 (95% CI 0.722-0.794). When tested on 2 additional data sets (ISIC 2020 and UQ), CNN-S ($P<.001$ and $P<.001$, respectively) and CNN-S2 ($P=.08$ and $P=.35$, respectively) still outperformed CNN-NS. When the CNNs were matched to the mean sensitivity and specificity of the teledermatologists on the

Danish data set, the models' resultant sensitivities and specificities were surpassed by the teledermatologists. However, when compared to CNN-S, the differences were not statistically significant (sensitivity: $P=.10$; specificity: $P=.053$). Performance across all CNN models as well as teledermatologists was influenced by image quality.

Conclusions: CNNs trained on standardized images had improved performance and, therefore, greater generalizability in skin cancer classification when applied to unseen data sets. This finding is an important consideration for future algorithm development, regulation, and approval.

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KEYWORDS

artificial intelligence; AI; convolutional neural network; CNN; teledermatology; standardized Image; nonstandardized image; machine learning; skin cancer; cancer

Introduction

Skin cancer (melanoma and keratinocyte cancer) is the most common type of cancer in fair-skinned populations, with the overall incidence and prevalence increasing worldwide [1]. In an effort to improve current prevention and detection practices, artificial intelligence (AI) has shown promise, at least in experimental settings.

In recent years, advances in machine learning and deep learning have led to increases in the research and exploration of potential applications in dermatology [2-6]. These advancements have led to the production of systems that can diagnose skin conditions through image analysis. With the help of clinical and dermoscopic images for training, convolutional neural networks (CNNs) have been able to compete and even outperform experienced dermatologists when diagnosing and classifying skin cancer [7-11].

Although these models perform well, they are often tested on images that they have already seen or come from the same data set in which the models were trained on, leading to an inflation in their performance [12]. When tested on externally sourced images, the performance of these models is reduced significantly, highlighting the models' poor generalizability [13].

Generalizability is an important factor that deserves careful consideration when assessing dermatology models. Generalizability refers to how well a model can apply the concepts it has learned from the available training data and implement these same concepts to data it has not seen before.

The method for collecting dermatology image data sets can be defined as nonstandardized and standardized. Nonstandardized image collection refers to images taken using multiple image capture devices and techniques. This method exposes the model to variation in image quality parameters, such as sharpness, brightness, polarization, magnification, color, and distance from lesion (for macroscopic images). Standardized image collection refers to images taken with the same image capture device and technique, resulting in a greater uniformity of images across a data set. It is unknown the extent to which uniformity (or lack thereof) of training images will affect the performance of the resultant CNN model.

Dermatology image data sets are generally not standardized and often collected retrospectively and contain images collected

with a variety of techniques and technologies. Theoretically, this variety increases the adaptability of the model and its ability to handle noisy and poorer quality data, thus increasing generalizability. However, with standardized image data sets, there is an expectation for greater consistency in image quality and, therefore, greater performance of the model. When considering the eventual implementation of a CNN model in a clinical setting, it is vital that the model's performance is impacted minimally by changes to the environment and patient demographic and variation in the presentation of disease. Identifying the factors that affect generalizability will increase the effectiveness of AI model implementation in practice. This retrospective comparative study assessed the generalizability of CNN models trained on standardized and nonstandardized images.

Methods

Test Sets, Study Population, and Image Selection

In this study, we compared the performance of CNNs trained on standardized and nonstandardized images when classifying skin cancer as malignant or benign on 3 separate external data sets.

Ethics Approval

This retrospective comparative study was approved by the Monash University Human Ethics Committee (Project ID 28130).

Architecture and Training of CNN Models

In all, 3 CNN models with the same architecture were trained on International Skin Imaging Collaboration (ISIC) 2019 [14-17] and MoleMap (MoleMap NZ Limited) [2] data sets. Model architecture used ImageNet pretrained ResNet-50 as a backbone (Figure 1) combined with a transformer [18,19]. The ResNet-50 backbone was incorporated because of the trade-off between accuracy and complexity. A transformer was also added to the model to overcome the limitation of CNN in the context of learning global images. The same 3 CNN models were then additionally trained with a ResNet-18 backbone on either the ISIC 2019 (CNN nonstandardized [CNN-NS]) or MoleMap (CNN standardized [CNN-S] and CNN standardized number 2 [CNN-S2]) data sets.

CNN-NS was trained on 25,331 nonstandardized ISIC dermoscopic images consisting of 8 skin conditions (Table 1). We define nonstandardized images as images that are taken

using multiple image capture technologies (Figure 2). CNN-S was trained on 177,475 standardized, teledermatologist-verified, clinical, and dermoscopic MoleMap images. This data set includes a total of 65 skin conditions organized into a 3-level hierarchical semantic tree (Table 1). This model was trained on standardized images taken using the same camera (DermLite

FOTO System). CNN-S2 was trained on 25,331 standardized, teledermatologist-verified, and dermoscopic MoleMap images consisting of 8 skin conditions (Table 1). CNN-NS and CNN-S2 were trained on the same number of images and skin conditions, only differing in the standardization of the images the models were trained on.

Figure 1. ResNet-50 backbone used by the CNN-NS, CNN-S and CNN-S2 models. CNN: convolutional neural network; Conv: convolutional layers; NS: nonstandardized; S: standardized.

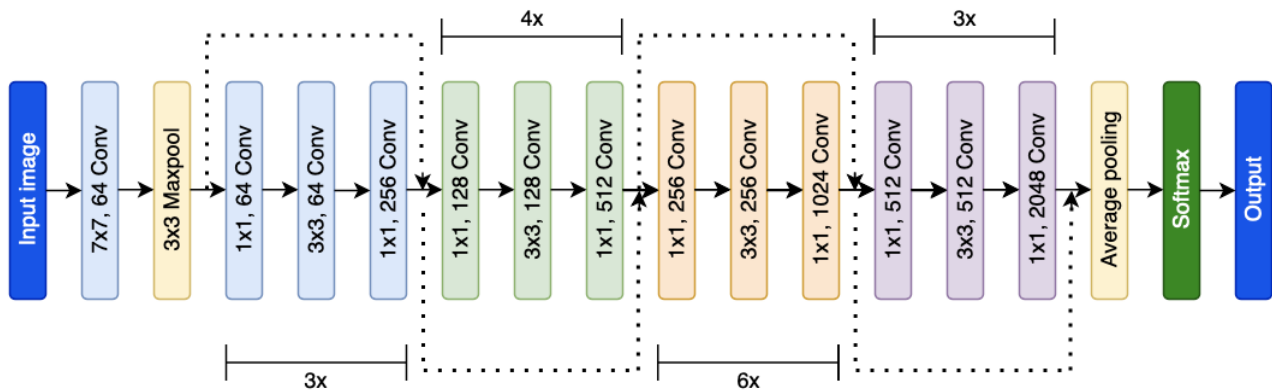


Table 1. Number of relevant skin diseases the CNN^a models were trained on.

Skin disease	CNN-NS ^b , n	CNN-S ^c , n	CNN-S2 ^d , n
Melanoma	4522	11,796	4522
Benign naevus	12,875	66,891	12,875
Benign keratosis	2624	22,100	2624
Dermatofibroma	239	4440	239
Basal cell carcinoma	3323	22,292	3323
Actinic keratosis and intraepithelial carcinoma	867	40,440	867
Squamous cell carcinoma	628	7060	628
Vascular proliferations	253	2456	253
Total	25,331	177,475	25,331

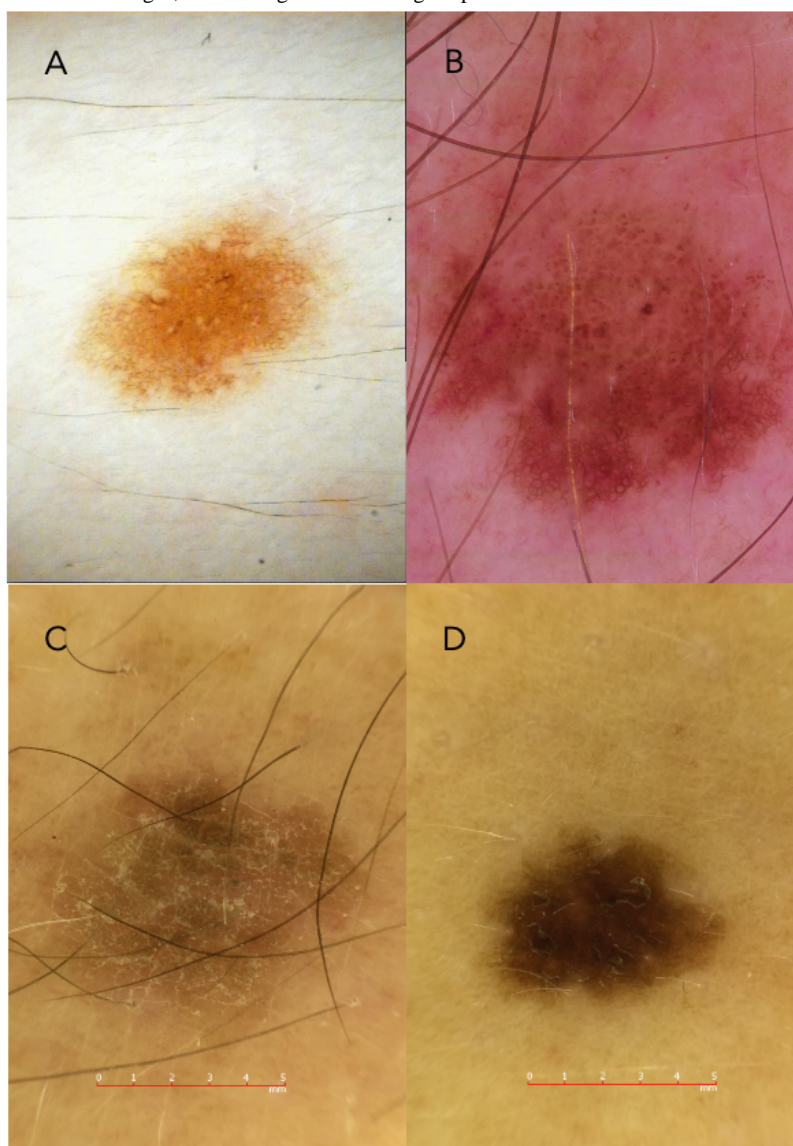
^aCNN: convolutional neural network.

^bCNN-NS: CNN nonstandardized.

^cCNN-S: CNN standardized.

^dCNN-S2: CNN standardized number 2.

Figure 2. Examples of standardized and nonstandardized images. Images A and B are nonstandardized images, taken using different image capture devices. Images C and D are standardized images, taken using the same image capture device.



Assessment of CNN Performance

CNN performance was assessed using 3 separate test data sets that were not used in model training.

Test Set 1

The Danish data set was provided by the Department of Dermatology and Allergy Centre, Odense University Hospital and collected between January 9 and October 31, 2018 [20]. General practitioners from 50 practices across southern Denmark were trained for 1 hour with the image capture equipment required to take images of lesions that are suspicious for malignant melanoma and nonmelanoma skin cancer. A total of 600 images were collected from 519 Danish patients, predominantly involving patients with Fitzpatrick skin types II and III, were used. The “ground truth” diagnosis was achieved

by histopathology, follow-up, or a single face-to-face evaluation (308 of the 600 lesions in the original data set were only seen once face-to-face). Images containing clinical features that could not be identified were removed from the data set, leaving 569 images. Lesion classification can be seen in Table 2.

The 569 images were taken using an iPhone 6 smartphone (Apple Inc) and a handyscope (FotoFinder Systems GmbH) with an overview, a close-up, and a dermoscopic image being taken of the lesions.

In total, 4 dermatologists were involved in the face-to-face and teledermatology evaluations of the 519 patients. The quality of the images was rated as “poor,” “fair,” or “good” by 3 allocators. Images were assigned to the different categories when there was agreement between 2 or more allocators.

Table 2. Skin disease breakdown of test sets 1, 2, and 3.

Classification, skin disease	Test set 1 (Danish data set), n	Test set 2 (UQ ^a data set), n	Test set 3 (ISIC ^b 2020 data set), n
Malignant			
Melanoma	20	21	584
Basal cell carcinoma	80	72	N/A ^c
Squamous cell carcinoma	5	7	N/A
Actinic keratosis and intraepithelial carcinoma	50	65	N/A
Other malignancy	3	N/A	N/A
Benign			
Benign keratosis	115	64	179
Vascular proliferations	45	1	N/A
Other	95	22	27,170
Benign naevus	156	170	5193
Total	569	422	33,126

^aUQ: The University of Queensland.

^bISIC: International Skin Imaging Collaboration.

^cN/A: not applicable.

Test Set 2

The University of Queensland (UQ) data set contained 422 dermoscopic images provided by The University of Queensland, Diamantina Institute, Dermatology Research Centre and captured using the EOS Rebel T6i camera (Canon) and ATBM master automated mole-mapping system (FotoFinder Systems GmbH) between 2016 and 2020, with all lesions diagnosed through histopathology (Table 2).

Test Set 3

The ISIC 2020 data set contained 33,126 dermoscopic images provided by the ISIC and collected from 3 continents between 1998 and 2020 [21]. The 33,126 images in the ISIC 2020 test set contained 59 images that overlap with the 25,331 images in the ISIC 2019 data set used for the training of CNN-NS.

All 3 test sets were imbalanced, with the Danish data set containing 411 benign and 158 malignant images, the UQ data set containing 257 benign and 165 malignant images, and the ISIC 2020 data set containing 27,131 benign and 5995 malignant images, which is reflective of the breakdown seen in a clinical setting. As the classification is binary, the imbalance had no effect on the study. Lesion classification can be seen in Table 2.

Statistical Analysis

Statistical analysis was performed using Python software (version 3.8.13; Python Software Foundation) and Stata statistical software (version SE 17; StataCorp). The primary outcome measures were sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC) for the binary classification of lesions.

For each input image, the CNNs provided a score between 0 and 1 representing the probability that the input image is malignant. In binary classifications, thresholds are applied to the CNN models to establish the point at which an input image is labeled malignant. This threshold is variable and allows for the manipulation of the sensitivity and specificity of the models.

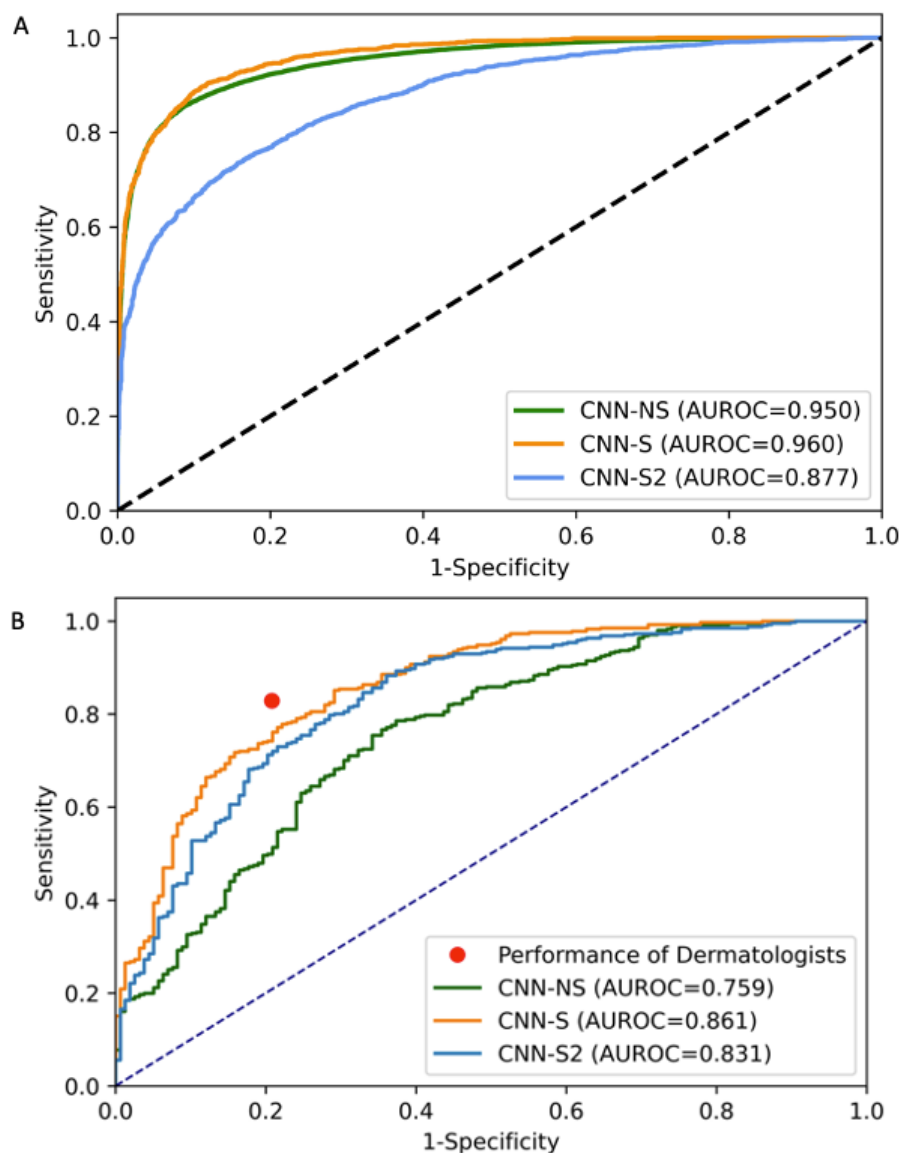
The performance was assessed by aligning the sensitivity and specificity of the CNN models to the teledermatologists' and by calculating the AUROC. AUROC allows for the direct comparison of different models regardless of the threshold applied. Delong nonparametric test was used to evaluate the statistical difference between AUROC values resulting from the same data set. Additionally, 95% CI for the AUROC was computed using 2000 stratified bootstrap replicates. McNemar test was used to compare the sensitivities and specificities of the CNN models. The 1-sample, 2-tailed *t* test was used to compare the mean sensitivities and specificities of the teledermatologists against the sensitivities and specificities of the CNN models. *P* values <.05 were considered to have statistically significant differences.

Results

Model Validation

During training, each model was internally validated on their training images. The model trained on nonstandardized images (CNN-NS) showed an AUROC of 0.950, whereas both models trained on standardized images (CNN-S and CNN-S2) showed an AUROC of 0.960 and 0.877, respectively (Figure 3).

Figure 3. Receiver operating characteristic curves and AUROC for (A) the 3 CNN models during training and (B) the performances of the teledermatologists and the 3 CNN models on the Danish test set. The receiver operating characteristic curves and AUROC of the CNN models in relation to the sensitivity and 1-specificity of the teledermatologists were tested on the 569 Danish test images. The teledermatologists' performance was greater than all of the CNN models. AUROC: area under the receiver operating characteristic curve; CNN: convolutional neural network; NS: nonstandardized; S: standardized.



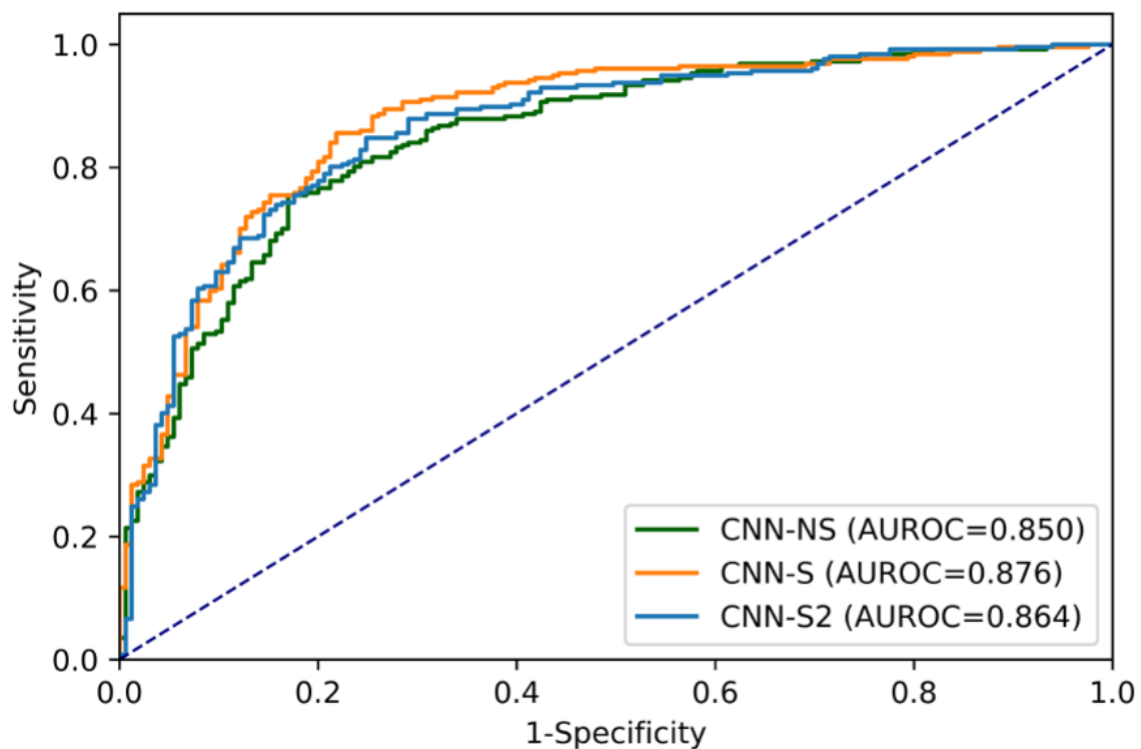
CNN Performance on Test Set 1

Each CNN model was tested on the externally sourced Danish test set of 569 images. CNN-NS performance fell with an AUROC of 0.759 (95% CI 0.714-0.802). CNN-S outperformed CNN-NS when examined on the Danish test set, with an AUROC of 0.861 (95% CI 0.828-0.894), showing significantly greater generalizability than CNN-NS ($P=.001$; Figure 3). CNN-S2, the standardized model trained on the same number of images as CNN-NS, also outperformed the model, showing an AUROC of 0.831 (95% CI 0.789-0.869; $P=.009$). Among the standardized models, CNN-S had the greatest AUROC (0.861 vs 0.831; $P=.06$).

CNN Performance on Test Set 2

When tested on the externally sourced UQ test set of 422 images, CNN-NS performed well with an AUROC of 0.850 (95% CI 0.812-0.887). CNN-S outperformed CNN-NS when tested on the UQ image set, with an AUROC of 0.876 (95% CI 0.842-0.911), again showing greater generalizability than CNN-NS ($P=.08$; Figure 4). CNN-S2 also achieved a slightly greater AUROC (0.864, 95% CI 0.828-0.900) compared to CNN-NS, though this was not statistically significant ($P=.35$). Among the standardized models, CNN-S had the greatest AUROC (0.8765 vs 0.8638), though the difference was not statistically significant ($P=.23$).

Figure 4. Receiver operating characteristic curves and AUROC for the 3 CNN models on The University of Queensland test set. AUROC: area under the receiver operating characteristic curve; CNN: convolutional neural network; NS: nonstandardized; S: standardized.

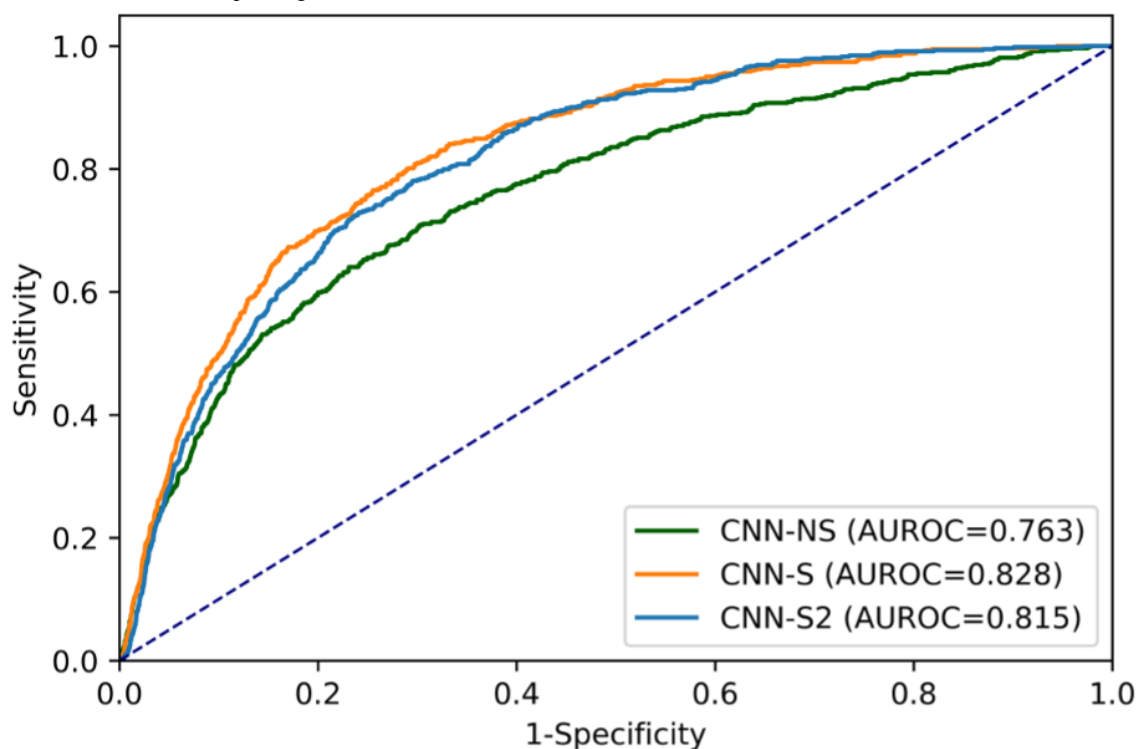


CNN Performance on Test Set 3

When tested on the publicly available ISIC 2020 test set of 33,126 images, the performance of CNN-NS was reduced, with an AUROC of 0.763 (95% CI 0.743-0.783). CNN-S significantly

outperformed CNN-NS when examined on the ISIC test set ($P < .001$), with an AUROC of 0.828 (95% CI 0.812-0.843), showing greater generalizability than CNN-NS (Figure 5). CNN-S2 also significantly outperformed the CNN-NS ($P < .001$), with an AUROC of 0.815 (95% CI 0.799-0.830).

Figure 5. Receiver operating characteristic curves and AUROC for the 3 CNN models on the International Skin Imaging Collaboration 2020 test set. AUROC: area under the receiver operating characteristic curve; CNN: convolutional neural network; NS: nonstandardized; S: standardized.



Teledermatologist Versus CNN Performance in Test Set 1

Teledermatologists (N=4) were split into 2 groups, teledermatologists 1 and teledermatologists 2. To evaluate the performance of the teledermatologists against the CNN models, we used the mean sensitivity and specificity of the 2 teledermatologist groups as a standard. On the Danish images, the teledermatologists achieved a mean sensitivity of 82.9% (95% CI 80.8%-85.0%) and specificity of 79.2% (95% CI 78.5%-79.9%).

The CNN models' malignancy threshold score can be manipulated, which can change the sensitivity and specificity of the models. To compare the performance of the models to each other, we first matched the sensitivity to that of the teledermatologists (82.9%). CNN-S achieved a specificity of 72% (95% CI 66.9%-75.9%), outperforming both CNN-S2 (62%, 95% CI 55.7%-65.3%; $P=.02$) and CNN-NS (45%, 95%

CI 38.4-49.6; $P=.001$). Additionally, CNN-S2 revealed a greater specificity than CNN-NS ($P=.001$). Next, we matched the specificity of each model to that of the teledermatologists (79.2%). CNN-S showed a sensitivity of 74.7% (95% CI 67.8%-81.8%), outperforming both CNN-S2 (71.5%; 95% CI 63.8%-78.4%; $P=.77$) and CNN-NS (56.3%; 95% CI 48.2%-64.2%; $P=.006$). Additionally, CNN-S2 revealed a greater sensitivity than CNN-NS ($P=.003$).

To compare models' performance to that of the teledermatologists, we compared the mean sensitivity (82.9%) and specificity (79.2%) of the teledermatologists to that of each model. This comparison revealed that our highest performing model (CNN-S) had a sensitivity (74.7% vs 82.9%; $P=.10$) and specificity (72.0% vs 79.2%; $P=.053$) comparable to that of the teledermatologists (Table 3). However, both CNN-S2 and CNN-NS had significantly lower specificity and CNN-NS had significantly lower sensitivity when compared to the teledermatologists (Table 3).

Table 3. Sensitivity and specificity of the CNN^a models when matched to the average performance of the teledermatologists.

	Specificity when matched to sensitivity, % (95% CI)	<i>P</i> value	Sensitivity when matched to specificity, % (95% CI)	<i>P</i> value
Teledermatologists (average)	79.2 (74.82-82.91)	Reference	82.9 (76.1-88.4)	Reference
CNN-S ^b	72 (67.4-76.3)	.053	74.7 (67.2-81.3)	.10
CNN-S2 ^c	65.2 (60.4-69.8)	.03	71.5 (63.8-78.4)	.07
CNN-NS ^d	46.7 (41.8-51.7)	.01	56.3 (48.2-64.2)	.03

^aCNN: convolutional neural network.

^bCNN-S: CNN standardized.

^cCNN-S2: CNN standardized number 2.

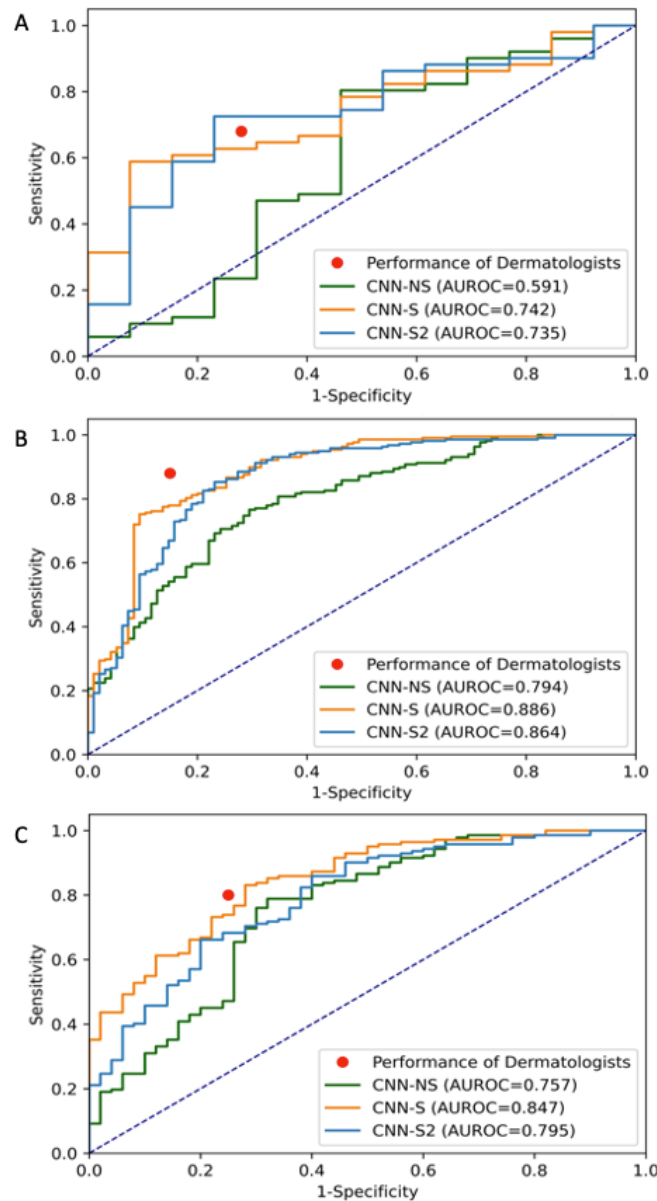
^dCNN-NS: CNN nonstandardized.

Effect of Image Quality on the Performance of Teledermatologists

When taking the image quality of test set 1 into consideration, the AUROCs of CNN-NS, CNN-S, and CNN-S2 increased as the quality of images improved (Figure 6). CNN-NS showed an AUROC of 0.591 (95% CI 0.389-0.778), 0.757 (95% CI 0.670-0.835), and 0.794 (95% CI 0.741-0.844) for images of

poor, fair, and good quality, respectively. CNN-S showed AUROCs of 0.742 (95% CI 0.602-0.864; poor quality), 0.847 (95% CI 0.792-0.879; fair quality), and 0.886 (95% CI 0.817-0.909; good quality), and CNN-S2 showed AUROCs of 0.735 (95% CI 0.578-0.873; poor quality), 0.795 (95% CI 0.721-0.861; fair quality), and 0.864 (95% CI 0.820-0.909; good quality).

Figure 6. Impact of image quality on the performance of the teledermatologists and AUROC of the CNN Models. The receiver operating characteristic curves and the AUROC of the CNN models and average sensitivity and 1-specificity of the teledermatologists on the Danish test set were split into (A) poor, (B) fair, and (C) good quality images. AUROC: area under the receiver operating characteristic curve; CNN: convolutional neural network; NS: nonstandardized; S: standardized.



Discussion

Principal Findings

Our results provide evidence that models trained on standardized images outperform and, hence, achieve greater generalizability than models trained on nonstandardized images. In recent years, advances in machine learning have led to the development of models that can compete and even outperform dermatologists in the classification of skin cancer [7-11]. Although these models have been shown to perform well when tested on a subset of images from their training data set, the generalizability of these models to images taken in different clinical settings and with different devices is unknown.

The impact that the varying image acquisition devices and techniques have on CNN model performance in dermatology has not been explored in the literature to date; however, the lack

of imaging standardization in dermatology has been highlighted. The collection, transfer, and storage of clinical and dermoscopic images are not standardized in dermatology and have implications on the creation of data sets for machine learning, the reproducibility of imaging, and accessibility to relevant metadata for the images [22,23].

The standardized models (CNN-S and CNN-S2) consistently outperformed the nonstandardized model (CNN-NS) on all test sets. The statistical significance was directly affected by the number of images in the 3 test sets, with fewer images in test set 2 resulting in a nonsignificant difference in performance. Larger test sets will have a more accurate measure of model performance, and this finding would need to be considered when reporting validation results.

The ISIC holds an annual challenge that invites contestants to create a model that is trained and tested on images provided by

the ISIC. In the AI community, the model that wins the ISIC challenge often holds a reputation as one of the best available. However, if tested on external data, the same performance is not guaranteed. If models are both trained and tested on the same set of images, then they are subjected to overfitting and thus poorer generalizability. The quality of a model should therefore be judged on its performance on multiple external data sets from varying population groups.

Several studies have looked at the performance of CNN models compared to the performance of dermatologists. These models perform comparably and even outperform dermatologists when classifying skin cancers. However, it is important to note that the images used in test sets are often taken from the same data sets used in the training of the models [7-11]. It is important when comparing models to dermatologists that the CNN is externally validated. This validation provides a clearer indication of the performance of the models in comparison to dermatologists and their ability to generalize to external data sets.

In our study, when tested on test set 1, the teledermatologists outperformed all models. Interestingly, CNN-S was trained on Australian and New Zealand patients and generalized well to the Danish images. There was no statistical difference between the sensitivity and specificity of the teledermatologists and the matched sensitivity and specificity of CNN-S. It is important to note that the Danish teledermatologists were predominantly trained on Danish skin and had access to metadata and multiple image viewpoints for a single lesion, which the models did not have access to. Previous studies have shown that the addition of metadata and inclusion of both macroscopic and dermoscopic images of a lesion can improve the performance of the model [24,25]. Therefore, incorporating these features into future models will be important and may level the playing field when assessing performance against teledermatologists' clinical assessment.

The Danish images used in our study were taken by general practitioners who were required to undertake training to use the image capture technology. However, there were some issues with the quality of the images: some lesions were not centered, several lesions may be present within a single image, and parts of lesions were not included within the image frame. As the image quality improved, the diagnostic performance of all models and teledermatologists also increased. This finding highlights the influence that image capture techniques and image quality can have on CNN models and teledermatologists' diagnostic ability. This finding is also a consideration when designing models for integration into web-based tools or mobile

apps with consumers as end users, as the quality of images taken by consumers on their smartphones will vary, especially in the absence of training.

Limitations

Our study has several limitations. First, the MoleMap data set used to train our 2 standardized CNN models was labeled by dermatologists; however, only very few images were biopsy proven. Given that histopathology is the gold standard for diagnosis, some of these images may have been mislabeled, which could have an impact on the performance of the models. Second, in test set 1 with 569 images, we only had access to 221 biopsy-proven images. The remaining 348 images in the test set 1 were labeled by dermatologists, which allows for the possibility of mislabeling. Third, the quality of the images in the training data sets (ISIC and MoleMap) and the type of image modality may have played a part in the performance of the models rather than the standardization of the images. It is important to consider that the quality of the camera used in the standardized MoleMap data set is less variable than the nonstandardized ISIC 2019 data set, which may have led to a discrepancy in the performance. CNN-S was trained on a combination of dermoscopic and macroscopic images, whereas CNN-NS and CNN-S2 were trained only on dermoscopic images. This combination of image modalities may have had an influence on the strength of the CNN-S model. Additionally, the models are complex, making it difficult to understand the process behind their decision-making (ie, a black box). This is an important limitation of the models and of this study and will be addressed through the incorporation of explainable AI techniques in our future models. Finally, in test set 1, the number of lesions in each group becomes small when divided into images of poor, fair, and good quality. In future studies, it would be better to evaluate a larger data set split among the quality groups to more confidently assess the relationship between image quality and CNN performance.

Conclusion

In this study, CNN models trained on standardized images based on dermoscopic and macroscopic modalities performed better than a CNN model with the same architecture trained on nonstandardized images when tested on external image data sets. This finding has important implications for model generalizability in the binary classification of skin cancer. In test set 1, image quality also had a direct impact on the performance of the models. For future algorithm training, development, and registration, it is important that model generalizability is considered through the evaluation of model performance on external image data sets.

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Conflicts of Interest

HPS is a shareholder of MoleMap NZ Ltd and e-derm Consult GmbH and undertakes regular teledermatological reporting for both companies. HPS is a medical consultant for Canfield Scientific Inc, MoleMap Australia Pty Ltd, and Blaze Bioscience Inc and a medical advisor for First Derm.

VM has received speaker fees from Novartis, Bristol Myers Squibb, Merck, and Janssen; conference sponsorship from L'Oreal; and grant funding from MoleMap paid to an institution for a clinical trial.

All other authors declare no other conflicts of interest.

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Abbreviations

- AI:** artificial intelligence
AUROC: area under the receiver operating characteristic curve
CNN: convolutional neural network
CNN-NS: CNN nonstandardized
CNN-S: CNN standardized
CNN-S2: CNN standardized number 2
ISIC: International Skin Imaging Collaboration
NHMRC: National Health and Medical Research Council
UQ: The University of Queensland

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Research Letter

Consent and Deidentification of Patient Images in Dermatology Journals: Observational Study

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consent; deidentification; journal; images; publication; privacy; readability; internet; dermatology; photo; privacy; patient rights; publication; publish; permission; publication; data sharing

Publication of patient images contributes to research and education in dermatology. However, it is important to protect patients' privacy and rights. The Committee on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE) have provided best practices and recommendations, respectively, for the protection of patients' rights in scholarly publications [1,2]. Nonetheless, requirements for the deidentification of patient images and for the acquisition of consent to publish such images vary across governing bodies and journals. Our objective was to describe leading dermatology journals' instructions regarding deidentification and consent to publish patient images as well as the content and readability of consent forms.

This study was exempt from institutional review board review as data were publicly available. Themes regarding the publication and deidentification of patient images, as well as the acquisition of consent, were extracted from COPE and ICMJE [1,2]. On June 9, 2021, the top 20 dermatology journals were determined using Google Scholar, which ranks journals based on the h5-index [3]. Guidelines, instructions for authors, submission checklists, and consent forms on the journals' websites were reviewed for criteria embodied by the themes extracted from COPE and ICMJE. Legal clauses in consent forms were summarized. Available consent forms were prepared and then assessed for readability using Microsoft Word (Microsoft Corporation), which calculates the Flesch-Kincaid Grade Level (FKGL) [4]. FKGL considers average sentence length and the average number of syllables per word to provide a corresponding US grade level rating [4].

A total of 19 (95%) journals' online instructions instructed authors to obtain written consent or permission for the publication of patient images (Table 1). The specific instances in which consent was required varied and included recognizable, identifying, identifiable, or possibly identifiable images; images that may, could be used to, could, or potentially identify the person; images in which the person could or can be identified, including by the patient; only if the patient's face is completely identified; or any or all patient images, regardless of whether a patient is or is not identifiable. Some journals provided specific guidance on identifiable features, such as facial features (n=5), tattoos (n=1), and jewelry (n=1). A total of 11 consent forms were identified from 10 journals (Table 2). All forms emphasized that the individual in a published image may be identified or that anonymity cannot be guaranteed. The average FKGL was 15.3 (range 12.1-22.8).

Instructions regarding the deidentification of patient images and acquisition of consent for publication differed across dermatology journals and incorporated various elements from COPE and ICMJE [1,2]. Most leading dermatology journals instructed authors to obtain written consent or permission to publish patient images. This is in contrast to a study that found that approximately 52% of dental, oral surgery, and otorhinolaryngology journals had a policy regarding clinical images [5]. Although readability scores should be used with caution, consent forms were difficult to read and were written, on average, at a college level based on an FKGL score of 15.3. It has been recommended that materials for patients should be written at the sixth-grade level or lower [6]. Consideration should be given to enhancing consent form readability, which

may improve patient understanding. Although we analyzed a small subset of journals from a specific subspecialty, our findings may raise awareness of the need to protect patients' right to confidentiality by implementing consistent policies for the publication of clinical images.

Table 1. Instructions for authors regarding deidentification, publication, and consent for patient images.

Criteria	Frequency among top 20 dermatology journals ^a , n (%)
Statement on requirement for consent or permission regarding patient images	19 (95)
Written or signed consent or permission required	18 (90)
Patient or patient representative to be informed that published content may be available on the internet	4 (20)
Patient or patient representative to be shown the manuscript that will be published	4 (20)
Publication of identifying information only if it is essential for scientific or scholarly purposes	11 (55)
Black bars or masking of the eyes or face are inadequate or not recommended	9 (45)
Recommend eye bar, black bar, or masking to anonymize	1 (5)
Recommend cropping of images or cropping performed by journal for deidentification	4 (20)

^aTop 20 dermatology journals per Google Scholar h5-index, where h is the largest number of published articles with at least h citations for each article [3] (listed in alphabetical order): *Acta Dermato-Venereologica*; *American Journal of Clinical Dermatology*; *Anais Brasileiros de Dermatologia*; *British Journal of Dermatology*; *Clinics in Dermatology*; *Contact Dermatitis*; *Dermatologic Clinics*; *Clinical, Cosmetic and Investigational Dermatology*; *Dermatologic Surgery*; *Experimental Dermatology*; *Indian Journal of Dermatology*; *International Journal of Dermatology*; *JAMA Dermatology*; *Journal of Dermatological Science*; *Journal of Dermatological Treatment*; *Journal of Investigative Dermatology*; *Journal of the German Society of Dermatology*; *Journal of the American Academy of Dermatology*; *Journal of the European Academy of Dermatology and Venereology*; and *The Journal of Dermatology*.

Table 2. Characteristics of patient consent forms for the publication of images.

Criteria	Frequency among consent forms ^a , n (%)
Patient or signer to be shown the manuscript that will be published, or patient or signer may waive this opportunity	6 (55)
Patient or signer informed that published content may be available on the internet	7 (64)
Consents to publication of case information or photograph	11 (100)
Understands they may be identified or indicates that anonymity cannot be guaranteed	11 (100)
Name of patient or name of person signing	11 (100)
Name of person who explained the form, author, or doctor	10 (91)
Contact information of person who explained the form, author, or doctor	2 (18)
Indicates that signing does not remove the right to privacy	2 (18)
Indicates that the patient or signer has the right to revoke consent, but after publication, revocation of consent is not possible	4 (36)
Statement on financial benefit or lack thereof	2 (18)
Release to Affiliates, Subsidiaries, Third Parties or Other Websites	9 (82)
Release of Claims Clause	3 (27)
Choice of Law Clause	2 (18)
In Perpetuity Clause	2 (18)
Defamation Clause	1 (9)
Attorney's Fees Clause	1 (9)

^aA total of 11 consent forms were provided online by the following 10 dermatology journals (listed in alphabetical order): *Acta Dermato-Venereologica*; *American Journal of Clinical Dermatology*; *Anais Brasileiros de Dermatologia*; *British Journal of Dermatology*; *Clinical, Cosmetic and Investigational Dermatology*; *Contact Dermatitis*; *Experimental Dermatology*; *JAMA Dermatology*; *Journal of Dermatological Treatment*; and *Journal of the American Academy of Dermatology*.

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Conflicts of Interest

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Abbreviations

COPE: Committee on Publication Ethics

FKGL: Flesch-Kincaid Grade Level

ICMJE: International Committee of Medical Journal Editors

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Research Letter

From the Cochrane Library: Interventions for Preventing Occupational Irritant Hand Dermatitis

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occupational irritant hand dermatitis; barrier creams; moisturizers; skin protection education; protective gloves; prevention; COVID-19; Cochrane; meta-analysis; irritant; dermatitis; hand; skin; dermatology; occupational; skin disease; prevention; protection

Occupational hand dermatitis, the most common work-related skin disease, is divided into irritant and allergic types [1]. Occupational irritant hand dermatitis (OIHD) is associated with repetitive wet work, contact with detergents and other chemicals, and prolonged glove wearing. OIHD frequently becomes chronic, exerts a major impact on quality of life, and may eventuate in disability or job loss/change. As such, its prevention is paramount.

In this paper, we summarize findings from a 2018 Cochrane systematic review and meta-analysis assessing the efficacy of strategies for primary prevention of OIHD [2]. Inclusion criteria specified randomized controlled trials (RCTs) of barrier creams, moisturizers, gloves, or educational programs involving employees without pre-existing OIHD working in high-risk fields. Databases were searched without language restriction through the end of January 2018. The primary outcomes were incidence of new-onset OIHD and frequency of intervention discontinuation owing to adverse effects.

In total, 9 RCTs were included, all conducted in Europe except for 1 from Singapore. The 2888 participants consisted of metalworkers, factory and slaughterhouse workers, cleaners and kitchen workers, hospital employees, and hairdressing apprentices, who ranged in age from 16 to 67 years. Interventions included barrier creams, moisturizers, barrier creams combined with moisturizers, and educational programs; no studies investigated protective gloves. The mean duration of the intervention was 11.6 months. Meta-analysis revealed that for all interventions, fewer participants developed OIHD compared to controls (Table 1); however, the differences were not statistically significant. The pooled analyses showed wide CIs, and the studies may not have been adequately powered to detect differences. None of the studies addressed the frequency of discontinuation of the intervention relating to adverse effects; however, recorded dropout reasons were unrelated to adverse effects; therefore, these strategies likely cause few or no serious side effects.

Table 1. Effects of interventions on development of occupational irritant hand dermatitis.

Intervention	Studies, n	Follow-up (months)	Participants, n	Proportion of participants developing OIHD ^a (%)		Relative effect, RR ^b (95% CI)	Quality of evidence ^c
				Patients	Controls		
Barrier creams ^d	4	6-12	999	29	33	0.87 (0.72-1.06)	Low
Moisturizers ^e	3	6-12	507	13	19	0.71 (0.46-1.09)	Low
Barrier creams + moisturizers	2	12 (median)	474	8	13	0.68 (0.33-1.42)	Low
Skin protection education	3	12-36	1355	21	28	0.76 (0.54-1.08)	Very low

^aOIHD: occupational irritant hand dermatitis.

^bRR: risk ratio

^cEvidence assessed using Grading of Recommendations, Assessment, Development and Evaluation Working Group criteria [3].

^dExamples of barrier creams used include Arretil, Ache Basis Creme, Excipial, Stoko Protect, and Travabon.

^eExamples of moisturizers used include Estolan, Keri Lotion, and Locobase.

There are several potential limitations of this Cochrane review. It included a small number of trials, mainly conducted in Europe, that used heterogeneous diagnostic criteria for OIHD. Additionally, no studies were designed to exclude patients with endogenous/atopic or allergic hand eczema (through patch testing). The ability to compare studies was limited due to variations in follow-up time and the nature of included occupations. Overall, the quality of the evidence was judged to be low.

This Cochrane review found that barrier creams and moisturizers may reduce the risk of developing OIHD to some degree, but there was insufficient evidence to support the effectiveness of

the evaluated workplace interventions in the primary prevention of OIHD. This does not imply that these interventions are *not* effective; on the contrary, barrier creams, moisturizers, and gloves continue to be broadly recommended as crucial measures for occupational skin protection, particularly in the current era of increased hand hygiene requirements during the SARS-CoV-2 (COVID-19) pandemic [4]. An important consideration is that suboptimal real-world use of prevention strategies may fail to demonstrate the efficacy observed in experimental settings [5]. To reach more certain conclusions, there remains a need for large and pragmatic worldwide RCTs using uniform inclusion and diagnostic criteria for OIHD conducted over extended follow-up periods (6-12+ months).

Conflicts of Interest

BLA has served as a research investigator or scientific advisor to AbbVie and Skin Research Institute, LLC. AGOL has received a research grant from Lilly; has served as a consultant for Genentech and Guidepoint, LLC; and has served in advisory boards for Janssen, Bristol Mayer Squibb, and Boehringer Ingelheim.

Editorial Notice

The views expressed in this paper are those of the authors and in no way represent the Cochrane Library or Wiley.

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Abbreviations

OIHD: occupational irritant hand dermatitis

RCT: randomized controlled trial

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Research Letter

From the Cochrane Library: Interventions for Acne Scars

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Acne vulgaris is a common skin condition that affects both adolescents and adults worldwide and frequently results in acne scars [1]. Atrophic scars are the most common type of acne scars and are caused by a loss of collagen that leads to depressions in the skin surface [2]. Currently, many options exist for acne scar treatment, including lasers, chemical peels, dermabrasion, injectable fillers, needling, subcision, punch excision, and punch elevation. However, providers and patients have few guidelines on how to optimize treatment. Because of the large disease burden and the physical, psychological, and social impact of acne scarring, it is important to provide guidelines for patients and providers on the safest and most effective treatments for this complication.

A 2016 Cochrane study [3] provided a comprehensive review of available treatments and their efficacy for treating facial atrophic acne scars. This review analyzed 24 randomized controlled trials (RCTs) and assessed two primary outcomes: participant-reported scar improvement and serious adverse events that caused withdrawal from the study. Secondary outcomes such as investigator-assessed scar improvement, patient satisfaction, quality of life, participant-reported or investigator-assessed short-term adverse events, and duration of postprocedure downtime were also measured.

Data from some of the included RCTs showed that fractional laser, chemical peeling (with and without skin needling), and injectable fillers were more effective than comparator treatments. Many studies that compared other treatment modalities to each other or to placebo concluded no significant difference in either participant-reported or investigator-assessed scar improvement. Tables 1 and 2 summarize the treatment comparisons of the 24 included RCTs.

This review [3] found moderate support for the use of injectable fillers in acne scar treatment and limited support for lasers, chemical peeling, radiofrequency, and skin needling. The authors could not recommend one treatment modality over another due to insufficient evidence supporting any particular treatment. The included studies were generally underpowered and had a high risk for bias due to lack of blinding and participants' expectations of treatment influencing improvement ratings. Assessment of acne scar treatment efficacy poses challenges secondary to differences in study parameters across studies, variable subjective improvement rating scales, and lack of long-term follow-up of scar improvement. Additional RCTs with larger study populations, sham and/or placebo trials, and standardized outcomes and improvement ratings are necessary to determine the efficacy of treatment [3].

Results of clinical trials published subsequent to this review [3] provide further insight. A double-blind, parallel, multicenter RCT [4] compared the effects of polymethylmethacrylate (PMMA) microspheres in collagen (ArteFill) injections to placebo (saline injections) as a treatment for acne scarring and reported treatment success in 64% of treated participants vs 33% of control participants after 6 months ($P=.0005$). Another multicenter, randomized, prospective study [5] compared combination microneedling with PMMA-collagen gel filler injections vs microneedling alone, and found the combination group had significantly improved acne scar scores at 24 weeks post treatment compared to the microneedling-alone group ($P=.0136$). These studies further support the efficacy of injectable fillers for treating acne scars, though additional research with long-term follow-up is warranted to assess the durability of outcomes.

Table 1. Comparison of interventions for acne scars.^a

Comparison ^a	Study details	Scar improvement	Adverse events	Quality of evidence	Risk of bias
Nonfractional nonablative (NFNA) laser vs placebo/no treatment	Frequency-doubled 532-nm Nd:YAG (neodymium:yttrium-aluminium-garnet) laser; within-individual study	Participant reported (PR): 53.6% improvement in acne scarring (range: 10%-90%); no data for untreated	None reported	Not assessed	High risk of detection bias
<i>Fractional laser (FL) vs NFNA laser</i>	CO ₂ FL vs Q-Switched 1064-nm Nd:YAG laser; parallel-group study	PR: 12/32 (FL) vs 3/32 (NFNA laser) participants reported >50% improvement in scars at 6 months (risk ratio [RR] 4.00, 95% CI 1.25-12.84)	Transient posttreatment burning sensation in the NFNA group; postinflammatory hyperpigmentation (PIH) reported in 16/64 subjects	Very low-quality evidence	Unclear risk of detection bias
FL vs placebo/no treatment	1540-nm Er:Glass FL; within-individual study	PR: 8/10 patients reported improved acne scars after 12 weeks; no data for untreated	Immediate pain and transient erythema post treatment	Not assessed	High risk of detection bias
FL vs placebo/no treatment	CO ₂ FL; within-individual study	PR: 12/12 subjects reported mild to moderate improvement in scars after 6 months; no data for untreated side	Mild to moderate pain, erythema, and wound formation	Not assessed	High risk of detection bias
FL vs radiofrequency (RF)	1550-nm Er:Glass FL vs fractional RF; parallel-group study	PR: 7/20 (FL) vs 9/20 (RF) participants reported >50% improvement in acne scarring at <24 weeks post treatment (RR 0.78, 95% CI 0.36-1.68)	Pain with FL greater than with RF; both groups reported erythema and edema; PIH in the FL group only	Very low-quality evidence	High risk of detection bias
FL vs RF	1550-nm Er:Glass laser vs fractional bipolar RF; within-individual	PR: mean improvement grade in acne scars after treatment; fractional laser (2.89, SD 0.57) vs RF (2.74, SD 0.73)	1/20 participants withdrew due to prolonged dyspigmentation negatively affecting quality of life	Not assessed	Unclear risk of detection bias
FL vs RF	10,600-nm CO ₂ FL vs fractional microplasma RF; within-individual	Investigator assessed (IA) ^c : acne scar improvement in FL (59.2%) vs RF (56.4%) (<i>P</i> =.93)	Posttherapy erythema, scaling, and PIH were more significant on the FL side	Not assessed	Not assessed
<i>FL vs combined FL with any active intervention</i>	10,600-nm CO ₂ FL alone vs same laser plus punch elevation; within-individual	IA ^c : 26/42 (FL) vs 31/42 (FL with punch elevation) investigators reported >50% acne scar improvement at <24 weeks (RR 1.45; <i>P</i> =.02)	Transient erythema, crusting, transitory burning after treatment, and mild PIH occurred with both interventions	Not assessed	Not assessed
FL vs combined FL with any active intervention	CO ₂ FL with saline vs CO ₂ FL with autologous platelet-rich plasma (PRP); within-individual	IA ^c : mean degree of clinical improvement for FL (2.3, SD 0.5) vs FL with PRP (2.7, SD 0.7)	Posttreatment crusting and edema lasted significantly longer on the FL-alone side than on the combined treatment side	Not assessed	Not assessed
FL vs chemical peeling (CP)	1550-nm Er:Glass FL vs chemical reconstruction of skin scars CP method; within-individual	IA ^c : average improvement grades after <24 weeks: FL (2.51) vs CP (2.44)	1/20 participants left the trial due to minor discomfort with treatment from pain and redness	Not assessed	Not assessed
FL vs combined CP with needling	Nonablative 1540-nm Er:Glass FL vs CP with trichloroacetic acid (TCA) 20% with skin needling; parallel-group	PR: 9/13 (FL) vs 9/13 (combined CP with needling) participants reported >50% acne scar improvement after 12 months (RR 1.00, 95% CI 0.60-1.67)	Pain, transient edema, and erythema were reported in both groups	Very low-quality evidence	High risk of detection bias
<i>CP vs placebo/no treatment</i>	Glycolic acid peels (at different concentrations) vs 15% glycolic acid cream vs placebo cream; parallel-group study ^d	IA ^c : significantly better response in the CP group vs placebo (<i>P</i> <.05)	CP group: 7 participants withdrew (intolerance to high concentrations, longer contact times of peeling agent); RR 5.45, 95% CI 0.33-90.14	Very low-quality evidence	High risk of attrition bias

^aStudies did not stratify patients based on acne severity (mild, moderate, severe), which may affect response to scar treatment.

^bItalicized studies indicate statistically significant study results.

^cPatient-reported scar improvement was not assessed in this study; investigator-reported scar improvement results were included.

^dBoth treatment arms (glycolic acid peels and glycolic acid creams) were combined into 1 treatment comparison group for analysis.

Table 2. Comparison of interventions for acne scars (continued).^a

Comparison ^a	Study details	Scar improvement	Adverse events	Quality of evidence	Risk of bias
Chemical peeling (CP) vs combined CP plus any active intervention	Deep peeling with oil phenol in a 60% concentration formula nonhydroalcoholic solution vs trichloroacetic acid (TCA) 20% with skin needling; parallel-group study	Participant reported (PR): 10/10 (CP) vs 8/10 (CP with needling) participants reported >50% acne scar improvement after 8 months (RR 1.24, 95% CI 0.87-1.75)	All participants reported pain and transient erythema in both groups	Very low-quality evidence	High risk of detection bias
CP vs needling	100% TCA chemical reconstruction of skin scars (CROSS) vs skin needling using dermaroller; parallel-group study	PR: 9/12 (TCA CROSS) vs 10/15 (skin needling) participants reported >50% acne scar improvement at 1 month (RR 1.13, 95% CI 0.69-1.83)	All participants reported pain and transient erythema in both groups; 6/12 participants in the peeling group experienced postinflammatory hyperpigmentation (PIH)	Very low-quality evidence	High risk of detection and attrition bias
Needling vs placebo/no treatment	Needling vs topical anesthetic cream; within-individual study	PR: 41% mean improvement in acne scars on the treated side	All participants reported pain, and transient erythema and edema were seen in all participants	Not assessed	Not assessed
Injectable fillers vs placebo/no treatment	Polymethylmethacrylate suspended in bovine collagen vs saline injections; parallel-group study	PR: 77% (injectable filler) vs 42% (placebo) of participants reported improved acne scarring (RR 1.84, 95% CI 1.31-2.59; $P<.05$)	Injection site pain, injection site tenderness, swelling, erythema, bruising, pain, itching, lumps or bumps, and discoloration	Moderate-quality evidence	Low risk of detection bias
Injectable fillers vs placebo/no treatment	Autologous fibroblasts vs vehicle control; within-individual study	PR: 43% of treated sides showed ≥ 2 -point acne scar improvement compared with 18% of the vehicle-control treated side ($P<.001$)	Participants in both groups reported mild to moderate erythema	Not assessed	Low risk of detection bias
Injectable fillers vs subcision	Injectable filler with natural-source porcine collagen vs 18-gauge Nokor subcision needle; within-individual study	PR: 3.5 (injectable filler) vs 3.9 (subcision) global improvement rate ($P=.12$)	Higher severity of bruising reported with subcision vs fillers	Not assessed	High risk of detection bias
Microdermabrasion (MDA) + aminolevulinic acid (ALA)-photodynamic therapy (PDT) vs MDA + placebo-PDT	417-nm blue light therapy plus MDA with 20% δ -ALA or vehicle solution	Investigator assessed (IA) ^c : 80% of participants showed acne scar improvement on the MDA + ALA-PDT side vs the MDA + vehicle-PDT side	None reported	Not assessed	Not assessed
Fractional laser (FL) vs FL	Er:YAG FL vs CO ₂ FL laser; within-individual	PR: 70% (Er:YAG) vs 60% (CO ₂) of laser sites were rated as showing >50% improvement in acne scarring ($P=.47$)	Participants reported erythema, edema, superficial crusting, and PIH	Not assessed	Not assessed
Photothermolysis vs FL	Nonablative 1550-nm erbium-doped fractional photothermolysis system (FPS) vs 10,600-nm CO ₂ FL system; within-individual	IA ^c : mean grade of improvement for FPS (2.0, SD 0.5) vs FS (2.5, SD 0.8) ($P=.158$)	Mean pain scores were significantly lower for FPS than with FL; side effects included crusting, scaling, redness, fluid retention, and hyperpigmentation	Not assessed	Not assessed
Pulsed dye laser (PDL) vs long-pulsed laser	Nonfractional nonablative (NFNA) PDL vs 1064-nm long-pulsed Nd:YAG (neodymium:yttrium-aluminum-garnet) laser; within-individual	IA ^c : acne scores improved by 18.3% (PDL) and 18.7% (Nd:YAG); no statistically significant difference between treatments	Reported adverse events included transient pain, erythema, and edema in treated areas	Not assessed	Not assessed
Long-pulsed Nd-YAG laser vs diode laser	NFNA 1320-nm long-pulsed Nd-YAG laser vs NFNA 1450-nm diode laser; within-individual	IA ^c : higher average clinical scores on 1450-nm diode laser-treated face side than on Nd-YAG laser-treated face side	All participants experienced posttreatment erythema, and some had PIH and discomfort with treatment	Not assessed	Not assessed

Comparison ^a	Study details	Scar improvement	Adverse events	Quality of evidence	Risk of bias
Long-pulsed Nd-YAG laser vs combined laser	Long-pulsed Nd:YAG laser vs combined 585/1064-nm laser; within-individual	IA ^c : acne scores improved by 27% (Nd:YAG) and 32.3% (585/1064-nm laser); no statistically significant difference	Reported adverse events included transient pain, erythema, and edema in both treated areas	Not assessed	Not assessed

^aStudies did not stratify patients based on acne severity (mild, moderate, severe), which may affect response to scar treatment.

^bItalicized studies indicate statistically significant study results.

^cPatient-reported scar improvement was not assessed in this study; investigator-reported scar improvement results were included.

Editorial Notice

The views expressed in this paper are those of the authors and in no way represent the Cochrane Library or Wiley.

This article is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2016, Issue 4, DOI: 10.1002/14651858.CD011946.pub2 (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

Conflicts of Interest

RPD is a joint coordinating editor for *Cochrane Skin*, editor-in-chief of *JMIR Dermatology*, a dermatology section editor for *UpToDate*, a social media editor for the *Journal of the American Academy of Dermatology*, and a podcast editor for the *Journal of Investigative Dermatology* (JID). He is a coordinating editor representative on Cochrane Council. TES serves as an editorial board member-at-large for *JMIR Dermatology*. ALC and RAH declare no conflicts of interest.

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Abbreviations

PMMA: polymethylmethacrylate

RCT: randomized controlled trial

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Research Letter

The Leading Authors in Three High Impact Dermatology Journals

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JAAD; Scopus; bibliometry; dermatology; research; publications; articles; bibliometrics

Recently in dermatology, the most influential scientists were reported [1,2]. Similarly, after analyzing the publications over 10 years (2011-2020), the top authors in the *Journal of the American Academy of Dermatology (JAAD)* were also described [3]. In this letter, we are reporting for the first time the top three authors in three world-class journals (ie, JAAD, *JAMA Dermatology* [JAMA-D], and *American Journal of Clinical Dermatology* [AJCD]). On July 24, 2022, the data was retrieved from the Scopus database, and the analysis was performed on RStudio (Bibliometrix/Biblioshiny) software (RStudio, PBC). We only analyzed research articles and excluded the year 2022. Scopus has been covering JAAD, JAMA-D and AJCD since 1979, 2013 and 2000, respectively. In total:

- JAAD published 17,065 research articles. A total of 93 authors published at least 30 articles (for a total of 2732 articles). In these publications, the authors were from 2307 universities in 65 countries.
- JAMA-D has published 1200 articles, of which 5975 authors from 1900 universities in 56 countries have contributed.
- AJCD has published 492 articles. In all publications, 1866 authors were from 838 universities in 45 countries.

During the analysis, authors were included from JAMA-D and AJCD if they had published at least 5 research articles.

There are several bibliometric indicators that can be used for analysis. For example, the h-index considers both the number of publications and citations. In other words, a dermatologist with 5 articles with 5 or more citations (each) will have an h-index of 5. The g-index is another interesting indicator. It represents the highest number “g” of articles that together received g^2 or more citations. A g-index of 10 indicates that the top 10 publications have been cited at least 100 times (10^2). The m-quotient (or m-index) considers both the h-index and the number of years. The m-index can be obtained by dividing the h-index by the number of years since the first publication of an author. For example, an h-index of 10 for an individual over 5 years means that the m-quotient is 2.

Our results differed from earlier reports [1-3], as they ranked the authors on the basis of the total number of publications and the h-index. We highlighted the most influential authors in all 3 journals on the basis of the total number of publications, total citations, h-index, g-index, and m-index. The data is presented in [Table 1](#). We also provide the list of the top 10 most productive universities and countries ([Table 2](#)).

The major limitations of this letter are name changes (variations in initials) and duplication of common names (authors and universities), which are not addressed. This may affect the ranking. We only relied on Scopus; other databases were not included in this study.

Table 1. The list of the top 3 authors in JAAD, AJCD, and JAMA-D.^a

Number of publications	Total citation	H-index	G-index	M-index
JAAD^{b,c}				
Feldman SR (n=127)	Feldman SR (n=12,778)	Lebwohl M (55)	Feldman SR (112)	Gelfand JM (1.895)
Lebwohl M (n=108)	Lebwohl M (n=10,127)	Feldman SR (48)	Lebwohl M (100)	Patel KR (1.8)
Paller AS (n=77)	Menter A (n=7754)	Gottlieb AB (39)	Paller AS (77)	Silverberg JI (1.769)
AJCD^{d,e}				
Piérard GE (n=10)	Silverberg JI (n=260)	Silverberg JI (8)	Piérard GE (10)	Simpson EL (1.75)
Silverberg JI (n=9)	Armstrong AW (n=244)	Armstrong AW (8)	Silverberg JI (9)	Chen Z (1.25)
Armstrong AW (n=9)	Feldman SR (n=218)	Feldman SR (7)	Armstrong AW (9)	Paller AS (1.25)
JAMA-D^{f,g}				
Mostaghimi A (n=30)	Margolis DJ (n=1159)	Armstrong AW (15)	Mostaghimi A (24)	Mostaghimi A (2)
Marghoob AA (n=21)	Schmults CD (n=1088)	Margolis DJ (14)	Marghoob AA (21)	Armstrong AW (1.5)
Margolis DJ (n=20)	Weinstock MA (n=1067)	Marghoob AA (14)	Margolis DJ (20)	Tkachenko E (1.5)

^aThe ranking is based on the number of publications, total citations, h-index, g-index, and m-index. The data was retrieved from Scopus on July 28, 2022, and analyzed on RStudio (Bibliometrix/Biblioshiny).

^bJAAD: *Journal of the American Academy of Dermatology*.

^cTotal publications: 26,185; total citations: 566,620 (citations of 20,000 documents); total h-index: 242 (of 20,000 documents); Impact Factor (2021): 15.48; CiteScore: 8.1; Scientific Journal Ranking (SJR; 2021): 1.948; Source-normalized Impact per Paper (SNIP; 2021): 2.512.

^dAJCD: *American Journal of Clinical Dermatology*.

^eTotal publications: 1418; total citations: 46,803; total h-index: 99; Impact Factor (2021): 6.23; CiteScore: 12.1; SJR (2021): 1.956; SNIP (2021): 3.024.

^fJAMA-D: *JAMA Dermatology*.

^gTotal publications: 3544; total citations: 46,377; total h-index: 82; Impact Factor (2021): 11.8; CiteScore: 12.5; SJR (2021): 2.412; SNIP (2021): 3.658.

Table 2. List of the top 10 most productive universities and countries.

Universities	Publications, n	Country	Publications, n
<i>Journal of the American Academy of Dermatology</i> (top 10 universities and countries)			
Mayo Clinic	171	United States	2395
Northwestern University Feinberg School of Medicine	162	Italy	155
Harvard Medical School	144	Canada	146
University of Pennsylvania	141	Germany	118
Icahn School of Medicine at Mount Sinai	134	Israel	88
University of Pennsylvania Perelman School of Medicine	131	Austria	65
University of California, San Francisco	126	United Kingdom	64
Wake Forest School of Medicine	113	Japan	58
Massachusetts General Hospital	110	France	55
Memorial Sloan-Kettering Cancer Center	87	Spain	45
<i>American Journal of Clinical Dermatology</i> (top 10 universities and countries)			
Harvard Medical School	94	United States	778
University of Pennsylvania	74	France	96
Brigham and Women's Hospital	73	United Kingdom	78
University of California, San Francisco	64	Germany	71
University of Pennsylvania Perelman School of Medicine	57	Spain	65
Northwestern University	56	Australia	62
Northwestern University Feinberg School of Medicine	54	Canada	57
Memorial Sloan-Kettering Cancer Center	48	Italy	50
Massachusetts General Hospital	40	Netherlands	46
Inserm	37	Denmark	43
<i>JAMA Dermatology</i> (top 10 universities and countries)			
Northwestern University Feinberg School of Medicine	17	United States	206
Icahn School of Medicine at Mount Sinai	15	Germany	46
Centre Hospitalier Universitaire de Liege	13	Italy	37
University of Texas MD Anderson Cancer Center	11	Turkey	35
University of Toronto	11	Canada	33
Friedrich-Schiller-Universität Jena	11	United Kingdom	29
Springer Nature	11	France	24
Ankara Numune Education and Research Hospital	10	New Zealand	24
Harvard Medical School	10	Belgium	19
University of Southern California	10	Spain	18

Conflicts of Interest

None declared.

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Abbreviations

AJCD: American Journal of Clinical Dermatology

JAAD: Journal of the American Academy of Dermatology

JAMA-D: JAMA Dermatology

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Short Paper

Social Media Impact of Articles Published by Dermatology Residents During Medical School: Cross-sectional Study

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Abstract

Background: The Altmetric score (AS) is a novel measure of publication impact that is calculated by the number of mentions across various social media websites. This method may have advantages over traditional bibliometrics in the context of research by medical students.

Objective: This study aimed to determine whether dermatology matriculants who graduated from higher-ranked medical schools published more articles with greater impact (ie, a higher AS) than those from lower-ranked institutions.

Methods: A PubMed search for articles published by dermatology residents who started medical school in 2020 was conducted. Demographic information and Altmetric data were collected, and medical schools were sorted according to US News' top-25 and non-top-25 categories.

Results: Residents who completed their medical training at a top-25 institution published more papers (mean 4.93, SD 4.18 vs mean 3.11, SD 3.32; $P<.001$) and accrued a significantly higher total AS (mean 67.9, SD 160 vs mean 22.9, SD 75.9; $P<.001$) and average AS (mean 13.1, SD 23.7 vs mean 6.71, SD 32.3; $P<.001$) per article than those who graduated from non-top-25 schools.

Conclusions: Our results indicate that students in top-25 schools may have greater access to research resources and opportunities. With a pass/fail United States Medical Licensing Examination Step 1 exam that may increasingly shift focus toward scholarly output from medical students, further discussion on how to create a more equitable dermatology match is essential.

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KEYWORDS

Altmetric score; bibliometrics; social media; dermatology; resident; medical student; publication; citation; Altmetric; research quality; publish; impact factor; Scientometrics

Introduction

The Altmetric score (AS) is a novel measure of publication impact that is calculated through an automated algorithm using the number of mentions on numerous social media websites, including Twitter and Facebook [1,2]. It may be advantageous to traditional bibliometrics in the context of analyzing research by medical students, as the AS peaks relatively quickly and measures qualitative data [3,4]. Currently, the relationship

between medical school rank and the quality of articles published by dermatology matriculants is unknown.

Methods

A PubMed search for articles published by dermatology residents who began medical school in 2020 was conducted. Residents who graduated from an osteopathic or foreign medical school, as well as those with a PhD, and articles without a DOI (digital object identifier) were excluded. Demographic information was obtained from publicly available profiles, and

AS data were collected from the Altmetric website [1]. Medical schools were sorted into US News' top-25 and non-top-25 categories, which were ranked partially based on the amount of federal funding received [5,6]. Kruskal-Wallis tests were used to analyze the association between medical school rank and research productivity.

Results

Postgraduate year 3 dermatology residents (N=401) published 1400 articles during medical school, averaging 3.69 per resident.

Table 1. Altmetric data for research by dermatology residents in medical school.

	Residents, n (%)	Publications, mean (SD)	Total AS ^a , mean (SD)	AS, mean (SD)
All residents	401 (100)	3.69 (3.7)	37.2 (111)	8.72 (30)
Medical school				
Top 25	127 (31.7)	4.93 (4.2)	67.9 (160)	13.1 (23.7)
Non-top 25	274 (68.3)	3.11 (3.3)	22.9 (75.9)	6.71 (32.3)

^aAS: Altmetric score.

Discussion

To our knowledge, this is the first study to use the AS to analyze the impact of articles published by dermatology residents during medical school. Prior groups have assessed the correlation between the AS and citation count [3,4]. Others have used traditional bibliometrics to evaluate medical student research productivity in various fields [7,8]. Since there is only a short time period when students can publish before applying for residency, metrics that take years to accumulate, such as citation count and the h-index, are not reliable for assessment of publication impact during medical school [3]. Given the rise of virtual information sharing due to the COVID-19 pandemic, alternative measurements of publication impact that rely on social media dissemination may become more pertinent.

Limitations to this study include the inability to capture all articles published due to name changes for various reasons

The mean total AS of articles by each resident was 37.2, with each of their articles averaging an AS of 8.72 (Table 1). Residents who completed their medical training at a top-25 institution published more articles (mean 4.93 vs 3.11, $P<.001$) and accrued a significantly higher total AS (mean 67.9 vs 22.9, $P<.001$) and average AS (mean 13.1 vs 6.71, $P<.001$) per article than those who graduated from non-top-25 schools.

including marriage and divorce, which may disproportionately affect the perceived productivity of female residents [9].

The new pass/fail United States Medical Licensing Examination Step 1 exam, while intended to cultivate the prospect of a holistic application process, has prompted concerns of an increasingly unhealthy focus on medical student scholarly output in research-heavy fields such as dermatology [10]. Our results indicate that students in top-25 schools may have greater access to research resources and opportunities. Students at non-top-25 institutions who cannot afford to take research years may not have a fair opportunity to compete with students from top-25 schools. While not a new phenomenon, the consequences of this new system appear to be antagonistic against the current movement toward equity in the field of medicine. Further discussion on how to create a more equitable match is essential. In a time when dissemination of research through the internet is growing at a rapid pace, we encourage future work to explore the utility of the AS in dermatology.

Conflicts of Interest

None declared.

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Abbreviations

AS: Altmetric score

DOI: digital object identifier

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Research Letter

Brachioradial Pruritus Due to Cervical Spine Pathology

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KEYWORDS

spine; pruritus; cervical; spine; pathology; neck; dorsolateral; pain; weather; symptoms; patient; disease; trauma; neurological; exam; clinic; case study; magnetic resonance imaging; skin; itching; itchy; itchiness; dermatology; dermatologist; case report

Introduction

Brachioradial pruritus is a skin condition that involves itching or pain most commonly involving the dorsolateral upper extremities. It is speculated that both cervical spine disease and sun-induced cutaneous nerve injury are important contributors, with varying degrees of presentation [1]. Patients often present with a history of sun exposure and are mostly middle-aged and female [2]. It has been postulated that neuropathic brachioradial pruritus may be the result of UV damage to nerve endings in an at-risk population with cervical spine pathology [3].

Case

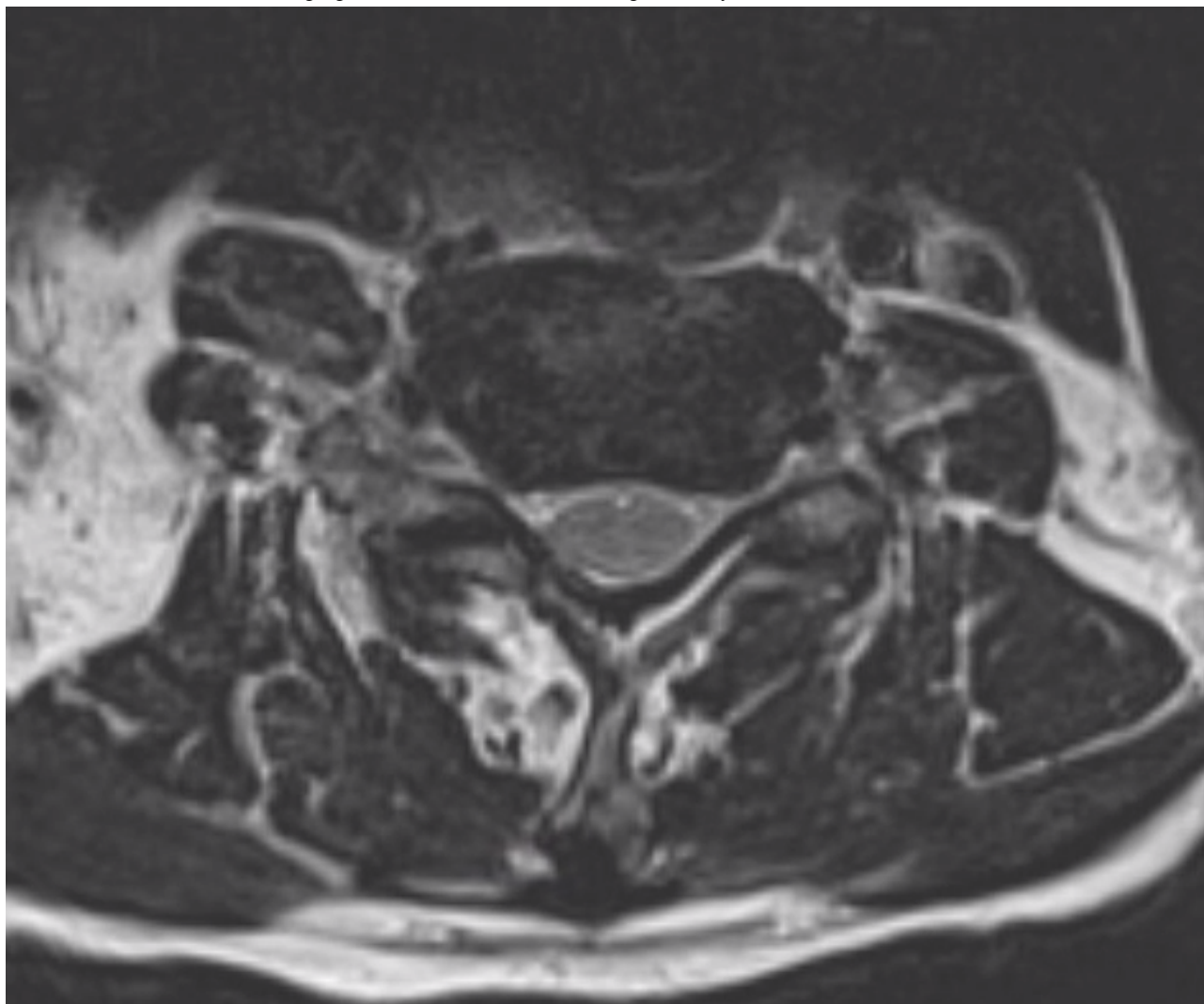
A 70-year-old female patient with no past medical history presented to the outpatient spine clinic with a 2-year history of intermittent pruritus predominantly along the bilateral dorsolateral forearm. Symptoms were often severe enough that scratching resulted in open sores on her forearms. However,

she denied any axial or radicular pain. She reported no known triggers except for flares occurring more frequently and with more severe symptomatology after sun exposure. The patient reported no prior dermatological diseases, familial pruritus, or trauma to the spine or extremities. She initially saw a dermatologist who deemed that the symptoms were not attributed to primary skin disease or inflammatory disorder. She then saw a rheumatologist who did not find any source of inflammatory disease. Magnetic resonance imaging of the C spine was obtained, and the patient was referred to a comprehensive spine center due to findings of bilateral neuroforaminal stenosis that was most severe at C4-C5 and C5-C6 (Figures 1 and 2). At the time of the spine clinic visit, she was asymptomatic; however, potential interventional options such as cervical epidural steroid injection were discussed in the event that her symptoms recurred. Prior to being evaluated in the spine clinic, she was taking prophylactic subsalicylate and loratadine due to mild alleviation of symptoms during a recent flare. The physical exam was unremarkable.

Figure 1. Midline sagittal view showing spondylosis that is worst at C5-C6 and C6-C7.



Figure 2. Axial view at C5-C6 showing significant neuroforaminal narrowing bilaterally.



Discussion

Itch is a complex neurologic phenomenon whose pathogenesis is only partially understood. It is speculated that irritation of spinal itch neurons caused by degenerative spinal changes leads to the spontaneous firing of damaged neurons, loss of the feedback mechanism for their descending inhibitory neurons, and loss of inhibitory interneurons that results in spinal hyperexcitability [3].

There are no established treatment guidelines for BPR. Various treatments have been described in the literature, each with mixed success. The conservative approach focuses on avoidance of

sun exposure and neuropathic medications. A case series of 3 female patients with an average age of 66 years demonstrated complete resolution of symptoms in 2 of the 3 patients treated with computed tomography-guided cervical root nerve block at the levels of greatest stenosis [4]. A recent case report of a patient with brachioradial pruritus who underwent multilevel cervical discectomy and fusion for cervical nerve root compression was found to be symptom-free afterward. Prior to surgery, he did receive temporary relief with epidural steroid injections [5].

This case is unique given that our patient presented with solely pruritus and without any history of pain related to her cervical spine pathology.

Conflicts of Interest

None declared.

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Case Report

Hepatic Metastasis Revealing a Melanoma of the Penis: Case Report

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Abstract

Melanoma of the penis is a rare tumor with a poor prognosis. We report the case of a 73-year-old patient with no significant medical history, admitted for deterioration of the general condition and bilateral inguinal lymph nodes. An abdominal ultrasound and thoraco-abdomino-pelvic CT (computed tomography) scan revealed metastatic liver nodules, the tumoral nature of which was confirmed by an anatomopathological examination. Further clinical examination revealed papular and ulcerated lesions of the penis located at the urethral meatus and glans penis. These lesions were biopsied and histologically assessed as melanoma. The contribution of imaging in penile tumors is generally not useful for diagnosis as clinical examination is key. However, it has its place in the assessment of locoregional and distant extension. In our case, it was the distant lesions that helped orient the diagnosis. The patient underwent immunotherapeutic treatment and is still alive 19 months after the diagnosis.

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KEYWORDS

melanoma; penis; immunotherapy; metastasis; lymph nodes; tumor; lesion; treatment; diagnosis

Introduction

Melanoma of the penis is a rare tumor with a poor prognosis [1-3]. Since 1859, nearly 200 cases have been reported in the literature, representing less than 1.4% of primary penile carcinomas [1,4-6]. It is generally located on the glans penis (55%), followed by the foreskin (28%), the penile body (9%), and the urethral meatus (8%) [2,7]. Melanoma in situ of the penis is much rarer [8,9] and usually occurs in older adults [2]. Imaging does not usually have a role in diagnosis, but it does play a role in the workup.

We present a case of multifocal melanoma of the penis in a 73-year-old man with inguinal lymph nodes and hepatic nodules revealed via an abdominal ultrasound and thoraco-abdomino-pelvic CT (computed tomography) scan performed as part of the etiological investigation of an altered general condition.

Case Report

The patient was 73 years old and had no previous history of illness. He presented with an altered general condition. The clinical examination revealed an altered patient with a World Health Organization performance status of 2, as well as visible and palpable bilateral inguinal adenopathy. The rest of the

examination was unremarkable. The patient underwent a standard biological workup (complete blood count, liver workup, and renal workup), where no abnormality was found.

He also underwent an abdominal ultrasound and a thoraco-abdomino-pelvic CT scan to look for a neoplastic cause. The latter showed secondary liver nodules (Figures 1 and 2) and multiple voluminous bilateral inguinal lymph nodes (Figure 2).

An echo-guided biopsy of one of the hepatic nodules was performed and came back in favor of a metastatic nature. A second and more thorough clinical examination was performed and revealed, in addition to inguinal lymph nodes, an ulcerated lesion of the urethral meatus with a brown spot background associated with brownish papules in the vicinity of the glans penis (Figure 3). Ultrasound of the penial ulceration showed a hypochoic and heterogeneous lesion (Figure 4). It should be noted that the patient is circumcised.

A biopsy of the urethral meatus lesion was then performed, and the anatomopathological examination with the

immunohistochemical profile was in favor of the melanoma type “not otherwise specified.” Indeed, it revealed a dermal lesion massively infiltrated by a malignant tumor proliferation, poorly limited epithelioma and rounded, with a clarified and abundant cytoplasm associated with foci of necrosis (Figures 5-7).

The proliferation infiltrated the surface epidermis. The Breslow index was estimated to be at least more than 4 mm with a level 4 on the Clark scale. After a multidisciplinary consultation meeting, surgery was not recommended because of hepatic and inguinal involvement and radical surgery would not have improved survival significantly [1]. Subsequently, immunotherapy was recommended, and the patient was referred to the oncology department where he underwent immunotherapeutic treatment (pembrolizumab 200 mg/week). The patient is still alive 19 months after the diagnosis, and the last control CT scan showed stability of the hepatic lesion and a reduction of the inguinal nodes.

Figure 1. Abdominal ultrasound showing (A) hepatic lesions (black arrow) and (B) bilateral inguinal lymph nodes, right and left sides.

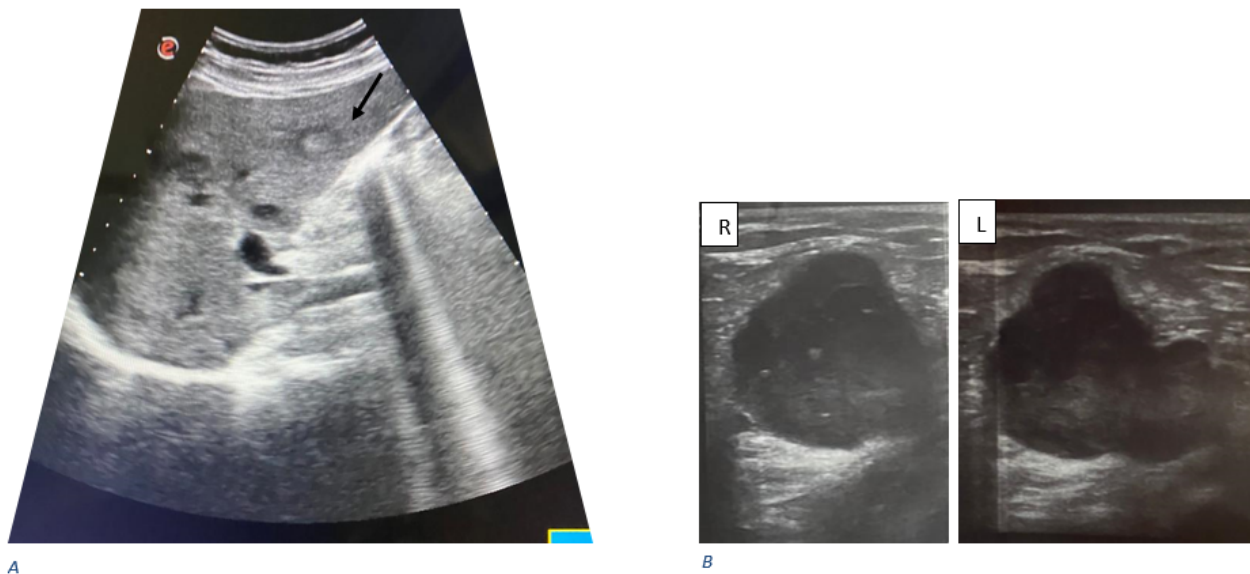


Figure 2. Thoraco-abdomino-pelvic CT scan showing hepatic lesions. CT: computed tomography.



Figure 3. (A) and (B) Ulcerated lesion of the urethral meatus, (C) erythematous and brownish papules on the left side of the penis gland, and (D) satellite brownish papules on the dorsal surface of the penis gland.



Figure 4. Ultrasound showing a penial hypoechoic and heterogeneous lesion.

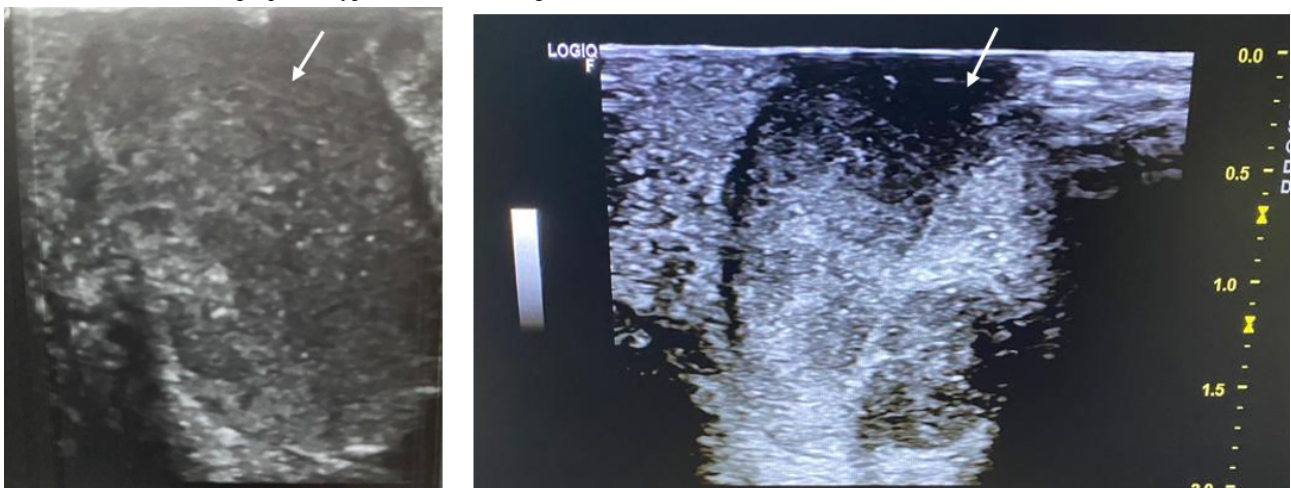


Figure 5. A histological image showing diffuse undifferentiated and ulcerated malignant tumor proliferation at $\times 40$ magnification with hematoxylin and eosin staining (black rectangle: epithelium ulceration; white circle: tumoral proliferation).

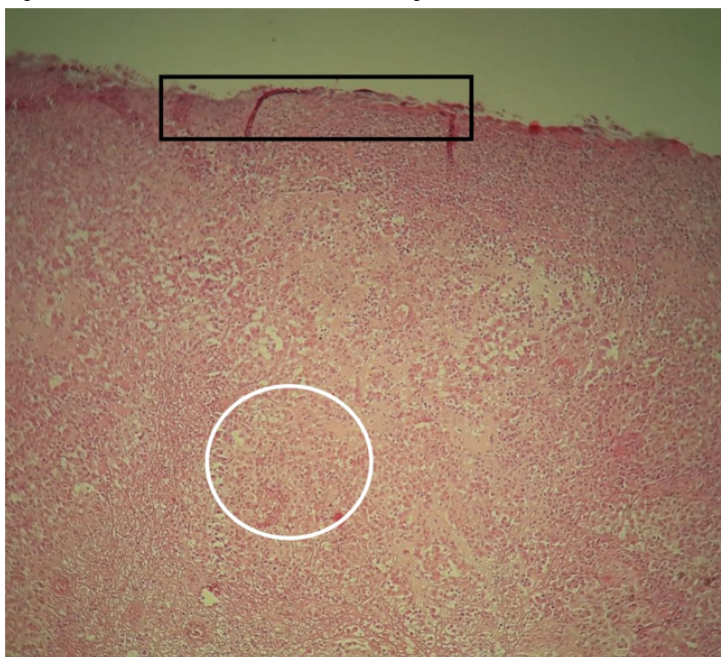


Figure 6. A histological image showing nests and lobules of highly nucleated epithelioid malignant tumor cells at $\times 200$ magnification with hematoxylin and eosin staining (yellow arrow: mitosis; black arrow: melanin pigment).

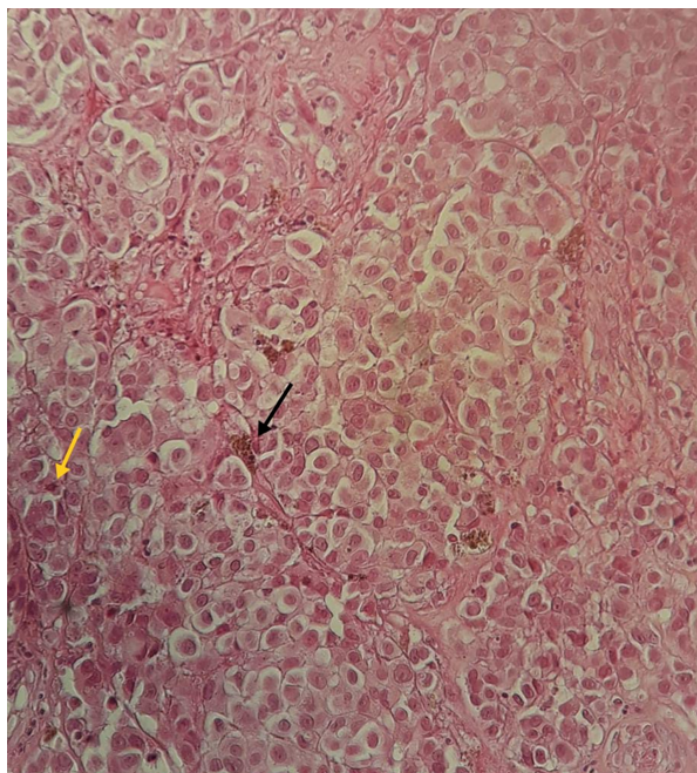
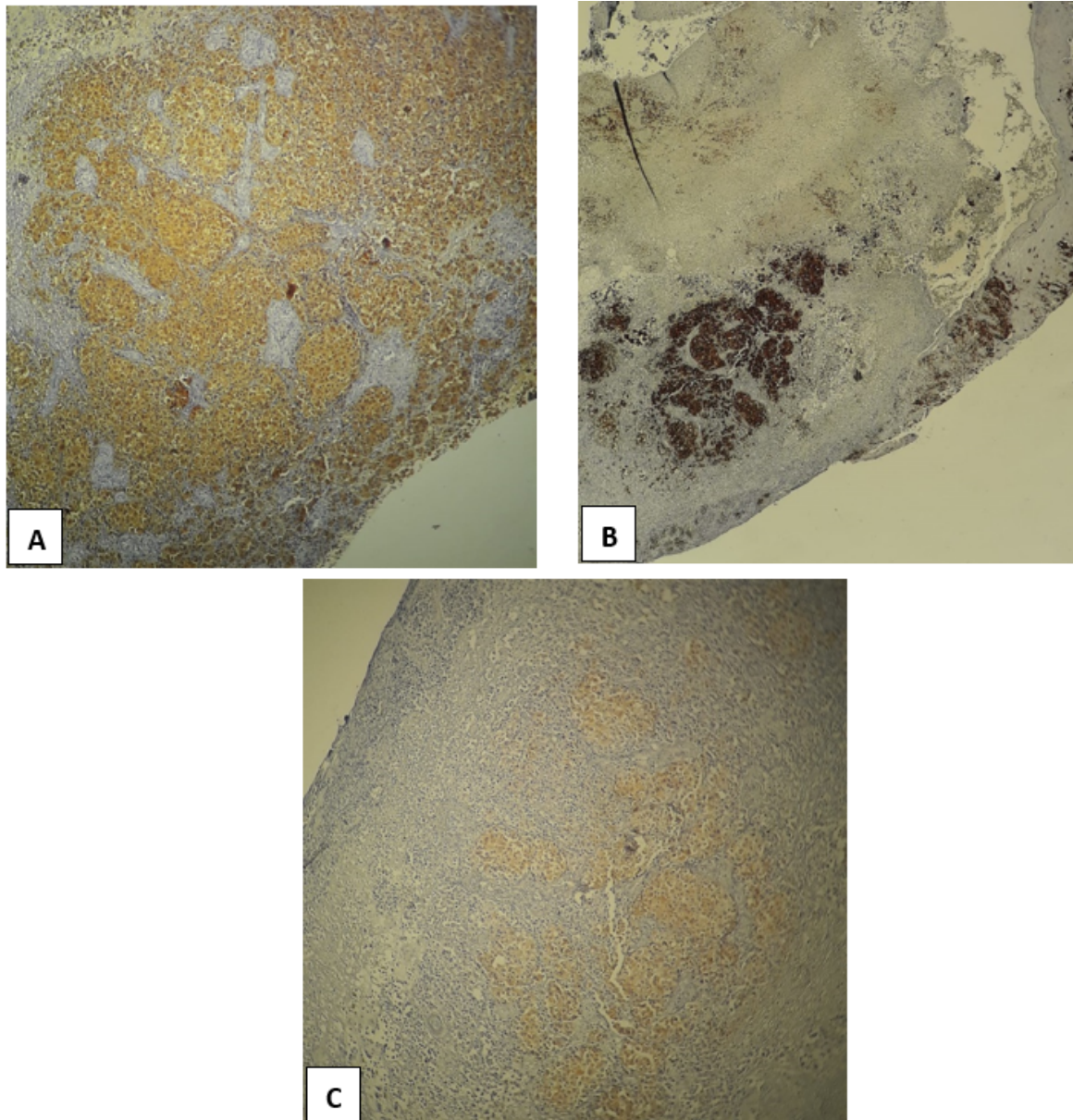


Figure 7. Immunohistochemical staining demonstrating staining with immunohistochemical melanoma markers (A) S100 protein, (B) HMB45, and (C) Melan-A.



Ethics Approval

The hospital's ethics committee approved this study, and patient consent was obtained.

Discussion

Principal Findings

Melanoma of the penis is a rare lesion and has a poor prognosis [10]. It is a tumor that generally occurs in older adults, with the peak incidence occurring between 50 and 70 years of age [1]. The peak frequency of cutaneous melanoma at other body sites is between 40 and 49 years of age [10].

One of the major difficulties of penile melanoma is early diagnosis, which remains challenging because the initial clinical presentation of melanoma is often indistinguishable from a benign lesion. Melanoma can present as a brown, reddish-black,

or bluish-pigmented lesion [10,11]. This is why any suspicious lesion should be biopsied early [10].

Various studies in the literature have reported melanomas of the penis and urethra [1,5,7,12,13]. In the latter case, the damage generally occurs in the fossa navicularis and more rarely in the pendulous, bulbous, and prostatic areas [1]. Only 5 cases of multifocal melanomas have been reported in the literature [1]. In our patient, melanomas were found in both the penis and urethral meatus.

There are no standard guidelines for the adequate staging of melanoma; however, most authors use a 3-stage system [14] to describe melanoma of the penis and the glans penis. Stage I refers to localized disease in the penis, stage II is melanoma involving the inguinal lymph nodes, and stage III refers to disseminated metastatic disease. Others use the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM)

cancer staging system [15]. The patient presented in this case report was assessed as having AJCC stage III (T4 N2 M1) melanoma of the penis.

Imaging does not usually play an important role in the diagnosis but rather in the assessment of extension, particularly in the search for distant lesions, and in the follow-up.

The prognosis of penile melanoma is generally poor [10], most often because it is diagnosed late, especially at the stage of metastasis as in the case of our patient.

The prediction of the evolution of melanoma is based mainly on the tumor thickness. It had been proven that some factors worsen the prognosis such as tumor thickness >3.5 mm, presence of ulceration and microsatellites, and tumor diameter >15 mm [10]. This type of tumor has a poor prognosis and metastasizes rapidly. It presents very variable clinical manifestations from macules to papules and nodules, all of varying color. The survival rate at 2 years and 5 years is 63% and 31%, respectively [10].

Early diagnosis is important because of the high risk of distant metastases. On the other hand, if the tumor is diagnosed early, it is potentially curable [16]. However, in common practice, it is usually revealed at a late stage.

The lack of public prevention and the sensitivity of the melanoma site make early diagnosis difficult. Treatment is based on surgery when there is no distant extension [17]. The gold-standard treatment is based on resection of the lesion while preserving the organ [1,2]. The search for sentinel and inguinal adenopathy is essential, and a lymphadenectomy is sometimes necessary [1]. The prognosis remains poor due to the lack of effective chemotherapy.

Conclusion

Malignant melanoma of the penis is a rare disease often associated with a high incidence of metastasis generally due to delayed diagnosis. The prognosis for survival is poor even when treated.

Conflicts of Interest

None declared.

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Abbreviations

AJCC: American Joint Committee on Cancer

CT: computed tomography

TNM: tumor-node-metastasis

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Case Report

Cutaneous Angiomyolipoma—A Distinct Entity That Should Be Separated From Classic Angiomyolipoma: Complete Review of Existing Cases and Defining Fundamental Features

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Abstract

Cutaneous angiomyolipoma is a rare mesenchymal tumor that is demographically, clinically, and immunohistochemically distinct from its renal and extrarenal counterparts. We present a case of cutaneous angiomyolipoma in the right retroauricular area of a 35-year-old male patient and provide a broad systematic review of the literature and the largest compilation of cutaneous angiomyolipomas reported to date. According to the findings presented in this review, we conclude that cutaneous angiomyolipoma should be completely separated from renal and extrarenal angiomyolipomas and therefore be considered a distinct entity in the classification of skin tumors.

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KEYWORDS

angiomyolipoma; cutaneous angiomyolipoma; cutaneous mesenchymal tumors; HMB-45

Introduction

Cutaneous soft tissue tumors are a heterogeneous group of neoplasms arising from different dermal and subcutaneous tissue components. Benign tumors vastly outnumber sarcomas [1].

Cutaneous angiomyolipoma (hereinafter described as “cutaneous AML”) is a benign tumor composed of varying proportions of thick-walled blood vessels, mature adipose tissue, and smooth muscle cells arranged in bundles, histologically identical to renal and extrarenal angiomyolipoma (hereinafter described as “classic AML”). Cutaneous AML is extremely rare and is not included in the latest 2018 World Health Organization (WHO) classification of skin tumors [1].

A total of 43 cases have been reported in English and Spanish literature to date; we present a new cutaneous AML in a 35-year-old male, which would represent the 44th case. We present the largest compilation of cutaneous AMLs, describe their clinical and morphological features, and contrast them with classic AMLs.

Our findings reveal that although they share similar histopathologic features, classic and cutaneous AML should be considered separate entities owing to their distinct demographic, clinical, and immunohistochemical features. Immunostains for melanocytic markers (such as monoclonal antibody HMB-45) are crucial in differentiating these 2 entities, being positive in classic AML [2-8] and negative in cutaneous AML. These differences allow us to conclude distinct histogeneses and

incorporate cutaneous AML into an independent category in skin soft tissue tumors.

Case Report

Case Overview

A 35-year-old male patient presented with a mass on his right ear, which progressively increased in size and became painful

Figure 1. Exophytic nodule localized in the postauricular region of the right ear, adjacent to the earlobe. Erythematous, soft to touch, mobile, measuring 1.7 cm in diameter. Epidermis is intact.



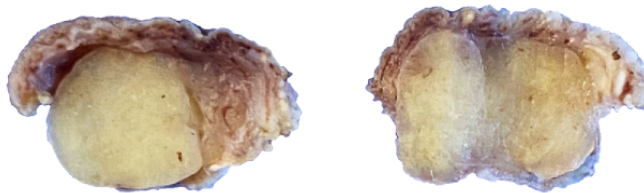
to touch after local trauma. He was otherwise in good health and had no clinical signs or familiar history of tuberous sclerosis complex (TSC) or classic AML. Physical examination revealed a nodular, erythematous, soft, mobile, subcutaneous mass in the right retroauricular area, which had a diameter of 1.7 cm (Figure 1). Clinical impression suggested a keloid scar versus skin appendage; thus, excision was performed by CO₂ laser.

Macroscopic Findings

The excisional skin biopsy showed a subcutaneous nodular mass covered by a rugged grayish-tan epidermal surface. At the cut

surface, a well-circumscribed, subepidermal, whitish-yellow, heterogeneous soft mass was present, measuring 1.3 × 0.6 cm (Figure 2).

Figure 2. Resected well-circumscribed mass measuring 1.3×0.6 cm with a heterogeneous whitish-yellow appearance.



Microscopic Features

Hematoxylin-eosin–stained sections revealed a well-circumscribed nodule, a surrounding fibrous pseudocapsule (Figure 3), small or medium blood vessels, adipose tissue, and bundled smooth muscle cells (Figure 3). Cellular pleomorphism, atypia, mitotic figures, and necrosis were absent. The tumor was in the junction between the reticular dermis and the hypodermis. The epidermal surface showed no significant histological changes.

Masson's trichrome staining revealed smooth muscle bundles (red), muscular blood vessels (red), stromal connective tissue (blue), and the fibrous pseudocapsule (blue) (Figure 4).

Immunohistochemical analysis using the Ventana BenchMark ULTRA platform with the UltraView detection system revealed positive staining for smooth muscle actin (SMA, clone 1A4) (Figure 4) and negative staining for the following melanocytic markers: anti-melanosome (monoclonal antibody HMB-45), MART-1 (Melan-A, clone A103) and Tyrosinase (clone T311; Figure 4). Both positive and negative controls were adequate for all studies.

Based on the findings, the case was diagnosed as a completely excised cutaneous AML. The patient had no recurrence at 1 month follow-up.

Figure 3. Low-power view demonstrating subcutaneous location and sharply demarcated border of the tumor (hematoxylin-eosin staining, $\times 10$ magnification). The tumor is composed of thick-walled blood vessels (black arrows), mature adipose tissue (arrowhead), and smooth muscle cells arranged in bundles (white arrow; hematoxylin-eosin staining, $\times 100$ magnification).

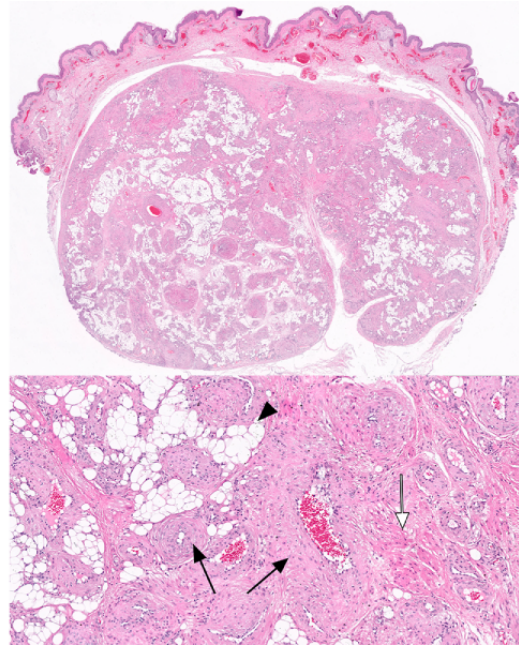
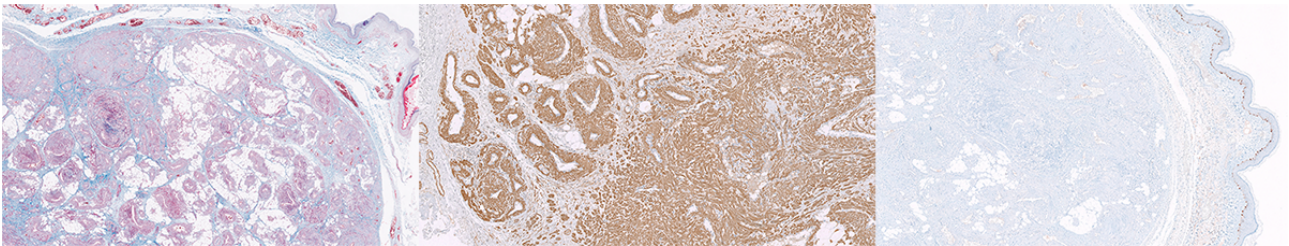


Figure 4. Smooth muscle bundles and vascular smooth muscle stained in red, and fibrous pseudocapsule stained in blue (Masson's trichrome stain, $\times 20$ magnification). Immunostaining showing the muscular components of the tumor (smooth muscle actin, $\times 100$ magnification). Completely negative immunostaining for melanocytic markers in the tumor, with a positive reaction in the epidermal melanocytes (Melanoma Cocktail: HMB-45, MART-1, and Tyrosinase; $\times 50$ magnification).



Discussion

Background

Soft tissue cutaneous tumors are a heterogeneous group of neoplasms originating from distinct dermal and subcutaneous tissue components. The most common benign mesenchymal tumors are lipomas, dermatofibromas (fibrous histiocytomas), vascular or smooth muscle lesions, and nerve sheath tumors. These tumors are usually superficial and small, measuring less than 5 cm, and present clinically as painless plaques or nodules with variable growth rates. Benign tumors are generally successfully treated with complete excision and rarely recur locally [1].

Cutaneous AML was first described by Argenyi et al [9] in 1986. Since then, according to a comprehensive review of English and Spanish literature (PubMed, SciELO, and Google Scholar) by searching the databases using the terms *cutaneous angiomyolipoma* and *cutaneous angiolipoleiomyoma* without date restrictions, 43 patients with cutaneous AML have been reported to date (Table 1) [10-39]. To our knowledge, our case is the 44th case of cutaneous AML described.

Data analysis from all reported cases of cutaneous AML reveals significant differences with classic AML and should therefore be classified as separate clinicopathological entities. To support this statement, we first describe classic AML, establish clinical and diagnostic criteria for cutaneous AMLs based on all cases reported to date, and finally contrast its characteristics with those of classic AML.

Table 1. Cutaneous angiomyolipoma: clinical and morphological features of all cases published to date.

Author (year)	Case	Sex (age in years)	Clinical diagnosis	Disease evolution time (years)	Location	Symptoms	Size (cm)	Microscopic findings	Melanocytic markers	Treatment	Recurrence
Argenyi et al [10] (1986)	1	Male (67)	Epidermal cyst	40	Right helix	Not specified (NS)	1×1	Adipose tissue (AT), blood vessel (BV), and smooth muscle (SM)	NS	Surgical excision	No recurrence at 5 years
Fitzpatrick et al [11] (1990)	2	Male (77)	Lipoma vs cyst	NS	NS	Asymptomatic	NS	AT, BV, SM, and pseudocapsule (PSC)	NS	Surgical excision	No recurrence
Fitzpatrick et al [11] (1990)	3	Male (63)	Giant cell tumor of tendon sheath vs mucoid cyst	0.5	Toe	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence
Fitzpatrick et al [11] (1990)	4	Male (50)	NS	NS	Head	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence
Fitzpatrick et al [11] (1990)	5	Female (59)	NS	NS	Elbow	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence
Fitzpatrick et al [11] (1990)	6	Male (52)	Lipoma	1	Hand	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence
Fitzpatrick et al [11] (1990)	7	Male (33)	Epidermal cyst	3	Toe	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence
Fitzpatrick et al [11] (1990)	8	Male (48)	Lipoma	0.16	NS	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence
Fitzpatrick et al [11] (1990)	9	Male (39)	Subcutaneous nodule	NS	NS	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence
Mehregan et al [12] (1992)	10	Male (49)	Epidermal cyst	NS	Right helix	NS	NS	AT, BV, SM, and PSC	Negative	Surgical excision	No recurrence
Rodríguez-Fernández et al [13] (1993)	11	Male (58)	NS	15	Elbow	Asymptomatic	4×3	AT, BV, SM, PSC, and atypia	NS	Surgical excision	No recurrence at 15 months
Ortiz-Rey et al [14] (1996)	12	Male (63)	Angioma	NS	Right preauricular area	Asymptomatic	1.5	AT, BV, SM, and PSC	Negative	Surgical excision	No recurrence at 11 months
Lee et al [15] (1996)	13	Male (32)	Lipoma vs epidermal cyst	5	Left earlobe	Asymptomatic	1.5×1.2	AT, BV, and SM	NS	Surgical excision	No recurrence
Val-Bernal et al [16] (1996)	14	Male (49)	Vascular tumor vs lipoma vs cyst	5	Right earlobe	NS	2.5×2	AT, BV, SM, and PSC	Negative	Surgical excision	No recurrence
Büyükbabani et al [17] (1998)	15	Male (38)	NS	10	Right retroauricular area	Asymptomatic	2.5×2.5	AT, BV, SM, and PSC	Negative	Surgical excision	2 previous recurrences in the same site following incomplete surgical excision
Büyükbabani et al [17] (1998)	16	Male (36)	NS	1.5	Nose	Asymptomatic	1.5×1.5	AT, BV, SM, and PSC	Negative	Surgical excision	NS
Castro-Forns et al [18] (1998)	17	Male (47)	NS	0.5	Nose	NS	1×0.7	AT, BV, and SM	NS	Surgical excision	NS

Author (year)	Case	Sex (age in years)	Clinical diagnosis	Disease evolution time (years)	Location	Symptoms	Size (cm)	Microscopic findings	Melanocytic markers	Treatment	Recurrence
Castro-Forns et al [18] (1998)	18	Female (65)	NS	NS	Lumbar	NS	5	AT, BV, and SM	NS	Surgical excision	NS
Obata et al [19] (2001)	19	Female (54)	Lipoma vs cavernous angioma vs arteriovenous hemangioma	5	Nose	Asymptomatic	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence at 1 year
Tsuruta et al [20] (2004)	20	Male (75)	Lipoma	10	Left lateral nose over nasal cartilage	NS	NS	AT, BV, SM, and PSC	NS	Surgical excision	No recurrence at 7 years
Carlos de la Torre et. al [21] (2004)	21	Female (35)	NS	10	Palm - hy-pothenar region	Painful at touch	1.5	AT, BV, and SM	NS	Surgical excision	NS
Beer et al [22] (2005)	22	Male (43)	NS	0.5	Left ear	Asymptomatic	0.4	AT, BV, and SM	Negative	Surgical excision	No recurrence at 23 months
Beer et al [22] (2005)	23	Male (56)	NS	NS	Chin	Fluctuation in size with time	0.6	AT, BV, and SM	Negative	Surgical excision	No recurrence at 23 months
Beer et al [22] (2005)	24	Female (44)	Cyst	0.25	Left helix	Fluctuation in size and warm, ticklish sensation	0.5 cm	AT, BV, and SM	Negative	Surgical excision	No recurrence at 23 months
Debloom et al [23] (2006)	25	Female (50)	Epidermoid cyst vs lipoma vs leiomyoma	5	Left anterior proximal thigh	Asymptomatic	2.8×2	AT, BV, SM, and PSC	Negative	Surgical excision	NS
Makino et al [24] (2006)	26	Female (16)	Vascular tumor	NS	Buttock	NS	2.5×1.5	AT, BV, SM, and poorly circumscribed	Negative	Surgical excision	No recurrence at 2 years
Hyo Chan Jang et al [25] (2006)	27	Male (57)	Epidermal cyst	4	Left retroauricular area	Asymptomatic	2×1.5	AT, BV, SM, and PSC	Negative	Surgical excision	NS
Singh et al [26] (2009)	28	Male (45)	NS	NS	Chin	Asymptomatic	1	AT, BV, and SM	NS	Surgical excision	NS
Sánchez-Estella et al [27] (2009)	29	Female (58)	Angioma	5	Left retroauricular area	Change in size according to the ambient temperature	1.5	AT, BV, SM, and PSC	Negative	Surgical excision	No recurrence at 26 months
Sánchez-Estella et al [27] (2009)	30	Female (52)	Angiomyolipoma	2	Left retroauricular area	Change in size according to the ambient temperature	1	AT, BV, SM, and PSC	Negative	Surgical excision	No recurrence at 5 months

Author (year)	Case	Sex (age in years)	Clinical diagnosis	Disease evolution time (years)	Location	Symptoms	Size (cm)	Microscopic findings	Melanocytic markers	Treatment	Recurrence
Shin et al [28] (2009)	31	Female (26)	Mucoid cyst	NS	Right helix	Asymptomatic	1×0.9	AT, BV, and SM	Negative	Surgical excision	No recurrence at 3 months
Mikoshiba et al [29] (2012)	32	Male (37)	Lipoma vs epidermal cyst	NS	Right earlobe	NS	1.7×1.6	AT, BV, and SM	Negative	Surgical excision	NS
Ammanagi, et al [30] (2012)	33	Female (3)	NS	NS	Anterior abdominal wall, below the umbilicus	NS	2.5	AT, BV, SM, and PSC	NS	Surgical excision	NS
Tchernev et al [31] (2014)	34	Female (66)	NS	NS	Right helix	NS	NS	AT, BV, and SM	NS	Surgical excision	No recurrence at 4 weeks follow up
Shim et al [32] (2014)	35	Male (45)	NS	NS	Right forehead	Asymptomatic	2×1.9	AT, BV, and SM	Negative	Surgical excision	No recurrence at 12-month follow-up
Han et al [33] (2014)	36	Male (36)	Vascular tumor	NS	Right nasal alar base	Asymptomatic	1×1	AT, BV, and SM	Negative	Surgical excision	NS
Yasar et al [34] (2014)	37	Male (67)	NS	10	Right earlobe	NS	2×2	AT, BV, and SM	NS	Surgical excision	No recurrence at 2 years
Carrau et al [35] (2015)	38	Male (13)	Neurofibroma	NS	First web space of the left foot	Asymptomatic	3.6×2.5	AT, BV, and SM	Negative	Surgical excision	NS
Kim et al [36] (2017)	39	Male (60)	NS	3	Glabella	Asymptomatic	2.3×1.7	AT, BV, SM, and PSC	Negative	Surgical excision	No recurrence at the 15 months
Mannan et al [37] (2019)	40	Male (36)	NS	NS	Right earlobe	NS	1.8×1.5	AT, BV, and SM	Negative	Surgical excision	NS
Araujo et al [38] (2020)	41	Male (32)	Epidermal cyst vs lipoma	4	Right earlobe	NS	1.3×1	AT, BV, and SM	Negative	Surgical excision	No recurrence at 44 months
Araujo et al [38] (2020)	42	Male (52)	Epidermal cyst vs lipoma	6	Right earlobe	NS	2.6×2.2	AT, BV, and SM	Negative	Surgical excision	No recurrence at 28 months
Oluwapelumi et al [39] (2020)	43	Female (11)	NS	11	Tip of nose	Recurrent mucus discharge, nasal blockage, and snoring	4×2	AT, BV (some cystically dilated), and SM	Negative	Surgical excision	No recurrence at 3 months
This study (2022)	44	Male (35)	Keloid scar vs skin adnexa tumor	Around 5 years	Right retroauricular area	Painful at touch	1.3×0.6	AT, BV, SM, and PSC	Negative	Surgical excision	No recurrence at 1 month

Classic AML

Overview

Classic AML is a benign mesenchymal tumor composed of thick-walled blood vessels, mature adipose tissue, and bundles of smooth muscle cells in variable proportions. It was previously described as a hamartomatous lesion; however, molecular studies revealed its clonality and neoplastic nature [2,8,40]. It presents almost exclusively in the kidney (99.7%) [2,8,41,42] and is therefore further classified as renal or extrarenal. Extrarenal AMLs (0.3%) have been reported in the liver (most common extrarenal AML) [43-51], spleen [52], retroperitoneum [53], nasal cavity [54], oral cavity [55,56], heart [57,58], colon [59], lung [60], vagina [61,62], ovary [63], fallopian tubes [64], mediastinum [65], spermatic cord [66], penis [67], bone [68], and skin [69].

Etiology and Pathogenesis

Classic AML belongs to the perivascular epithelioid cell tumor (PEComa) family, which also includes lymphangiomyomatosis [40,70-73], clear cell “sugar” tumor [40,74-79], clear cell myomelanocytic tumor of the falciform ligament or ligamentum teres [80,81], abdominopelvic sarcoma of PECs [3-7], and cutaneous PEComa [82-85]. Classic AML is the most common PEComa [40].

Although all these tumors have distinct histologic features, they all originate from perivascular epithelioid cells, which have the peculiarity of coexpressing both melanocytic and myogenic markers. Therefore, these tumors probably originate from a cell with myomelanocytic differentiation, although no normal counterpart for this cell has been described [40,86].

The majority of classic AMLs are sporadic (80%). In comparison, up to 20% of them are associated with TSC [87,88]—a rare, autosomal dominant, multisystemic syndrome characterized by cutaneous abnormalities such as facial angiofibromas, ash-leaf macules, and shagreen patches—and diverse tumors, including classic AML (80% of patients with TSC) [2,40], subependymal giant cell tumor, cardiac rhabdomyoma, and lymphangiomyomatosis (LAM) [8,89]. Biallelic mutations in *TSC1* (~25%, hamartin in 9q34) and *TSC2* (~75%, tuberlin in 16p13.3) [8,40,90-92] via point mutations, deletions, missense mutations, or copy neutral loss of heterozygosity [88,93] cause mTOR hyperactivation and consequently stimulate cell growth. Sporadic AML has also been associated with *TSC2* mutations [8,40,93]. TSC-associated classic AML tends to be bilateral and multifocal, while sporadic AML cases are isolated and unilateral [3,5,41].

Classic AML can also be associated with adult polycystic kidney disease, neurofibromatosis type 1 (NF1), and von Hippel-Lindau syndrome [32].

Epidemiology

Classic AML accounts for less than 1% of renal tumors; however, it is the most common renal mesenchymal tumor [8,87]. Sporadic classic AML has a female predilection (4:1) and occurs in patients between the age of 40-60 years, whereas TSC-associated classic AML has no gender predominance and occurs in patients between the age of 30-40 years [2,8,40,94].

Clinical Features

Most classic renal AMLs are asymptomatic and incidentally detected through imaging, surgery, or autopsy [8]. However, more than 80% of those larger than 4 cm are associated with abdominal or flank pain, hematuria, nausea, vomiting, fever, mass palpation [2,8], and renal failure (on rare occasions) [87], or new-onset hypertension [8]. Half of the symptomatic cases develop spontaneous bleeding, which may result in massive retroperitoneal hemorrhage and hypovolemic shock [2,8,41,95,96]. Rupture and bleeding during pregnancy are well-recognized complications [97,98]. Hence, tumors larger than 4 cm warrant prompt surgical intervention.

Radiologic Findings

Classic renal AML is easily diagnosed with uncontrasted computed tomography (CT) or magnetic resonance imaging (MRI) because of its abundant fat tissue. In 2016, Song et al [99] established a radiologic classification of renal AML as being “fat-rich,” “fat-poor,” or “fat-invisible”; the latter can have overlapping radiologic features with renal cell carcinoma and may often require percutaneous biopsy for adequate diagnosis [99-102].

Macroscopic Features

Classic AML is a yellow-white, smoothly rounded tumor with well-circumscribed, nonencapsulated borders. Its appearance varies depending on the proportion of adipose, vascular, and muscular components present [2-8,41]. Tumor size is variable, with those of sporadic cases ranging 1-30 cm (median 9 cm), while those of TSC-associated cases are usually smaller and can be multiple [2,103].

Microscopic Features

Classic AML comprises the characteristic triad of thick-walled blood vessels devoid of lamina elastica, mature adipose tissue, and bundles of spindled or epithelioid smooth muscle cells [2-8,41,42,87]. Hemorrhage and necrosis are commonly detected [8].

There are several histologic variants, including microscopic AML (absent thick-walled blood vessels) [104,105], intraglomerular AML (epithelioid smooth muscle cells intermixed with a few adipocytes in capillary tufts) [106,107], AML with epithelial cyst (cysts, “cambium-like” stromal cells, solid smooth muscle predominant areas, prominent lymphovascular network, and rare adipose tissue) [108,109], lymphangiomas of the renal sinus (plaque-like mass in the renal pelvis) [110], sclerosing AML (cords and trabeculae of bland epithelioid cells in abundant sclerotic stroma) [111], and epithelioid AML (EAML) [40,87,104,112]; the latter has distinct implications that require further description.

EAMLs (5%-7% of classic AML) require more than 80% of epithelioid morphology [8,40,104], consequently reducing the proportion of blood vessels and adipose tissue. It has varying degrees of nuclear atypia and may contain multinucleated giant cells. This rare subtype is potentially malignant and may exhibit aggressive behavior such as recurrence, invasion into the inferior vena cava, and metastasis (to the lungs, bone, and liver) [8]. Brimo et al [113] established a model to predict malignant and

aggressive clinical behavior in EAMLs when finding 3 or more of the following: $\geq 70\%$ of atypical epithelioid cells, ≥ 2 mitotic figures per 10 high-power fields, atypical mitotic figures, and necrosis. Hence, EAMLs must be monitored closely.

Immunohistochemistry

Classic AML is typically positive for melanocytic markers (95%) such as HMB-45 (expressed in a patchy pattern), Melan-A, Microphthalmia transcription factor, and Tyrosinase [2,8,40,114]. Smooth muscle cells are also immunoreactive to myogenic markers such as SMA, Calponin, and Desmin [8]. Other positive markers include cathepsin K [2,8,40] and, less frequently, CD117, CD68, S-100, estrogen receptor, and progesterone receptor (more common in the epithelioid variant) [2,8,40,115-117].

Treatment

Surgical management is recommended in AMLs with a tumor size greater than 1 cm, symptomatic patients, or those with a high risk of tumor bleeding or rupture. Some tumors have been treated with embolization. In some cases, medical therapy with mTORC1 inhibitors, such as sirolimus, has shown a positive clinical response and prevented renal failure [40,101,118,119].

Table 2. Cutaneous versus classic angiomyolipoma.

	Classic angiomyolipoma	Cutaneous angiomyolipoma
Demographic data	Predominant in females	Predominant in males
Etiopathogenesis	Perivascular epithelioid cell tumor; 20% associated with tuberous sclerosis complex	One case associated with neurofibromatosis type 1
Clinical	Almost exclusively in the kidney; median size 9 cm	More frequent in the ear; median size 1.5 cm
Morphology	Epithelioid angiomyolipoma with varying atypia, mitosis, and necrosis	No atypia, mitosis, or necrosis
Immunohistochemistry	Positive melanocytic markers	Negative melanocytic markers
Prognosis	Epithelioid angiomyolipoma can recur, metastasize, and cause cancer-related death	Resolution following complete surgical excision

Epidemiology

Unlike its classic counterpart, cutaneous AML occurs predominantly in males (70%). The age range is wide (2-77 years), with a peak incidence between the age of 30-50 (median 48) years.

This tumor occurs predominantly in the head (76%) but has also presented in the limbs (22%) and abdomen (2%). Of the head tumors, the ear was the most frequent location in 62% of cases, followed by the nose in 19%, and, less frequently, in the forehead, chin, and eyelid (19%).

Clinical Features

Most patients are asymptomatic, presenting only with a visible or palpable nodular lesion with slow growth, ranging from 2 months to 40 years (median 5 years). Some patients experience tumor size fluctuation over time or that associated with environmental temperature changes (clinical manifestation of the vascular component of the tumor) [22,28], pain (probably associated with increased sensitivity due to location or trauma)

Asymptomatic patients with AMLs smaller than 1 cm and those with significant comorbidities with AMLs smaller than 3 cm should be followed up periodically with CT or MRI [101].

Prognosis

Recurrence in classic AML is rare; however, approximately 25% of cases of EAML with atypia can recur, metastasize, and cause cancer-related death [8,114]. In a series of 41 cases of pure (monotypic) epithelioid cell PEComa neoplasms, Nese et al [120] observed recurrence in 17%, metastasis in 49%, and cancer-related death in 33% of cases.

Cutaneous AML

Overview

Cutaneous AML is demographically, clinically, and immunohistochemically distinct from its classic counterpart (Tables 1 and 2). Cutaneous AML, previously termed cutaneous angiolipoleiomyoma [11,24,34], is a rare, benign tumor with varying proportions of thick-walled blood vessels, adipose tissue, and smooth muscle cell bundles.

[21], and obstructive symptoms related to specific sites (such as nasal cavity) and large tumor size [39].

In the majority of cases, cutaneous AMLs are clinically misdiagnosed. The most common clinical diagnoses are cystic lesions (35%, mainly epidermoid cysts), lipomas (28%), and benign vascular tumors (17%; Table 1), the latter two being consistent with the tumors' components.

No cases of cutaneous AML have been associated with TSC to date. Only one case of AML in the skin in a patient with TSC has been reported [69]; however, this tumor had all the features of classic AML (including expression of melanocytic markers), which suggest classic AML with skin extension rather than a true cutaneous AML. A sole case of true cutaneous AML was reported in a patient with NF1 [35].

Radiologic Findings

Owing to its superficial location and easily accessible surgical approach, imaging studies are usually unnecessary for diagnosis. In the few cases reported, CT and MRI confirmed adipose and

vascular components [33], similar to classic AMLs' radiologic findings.

Macroscopic Features

Cutaneous AMLs are well-circumscribed, whitish-gray dermal tumors, measuring 0.4-5 (median 1.5) cm, generally smaller than their classic counterpart (median 9 cm).

Microscopic Features

Histologically, most cases are well-circumscribed, with an admixture of small to medium, thick-walled, muscular blood vessels (some dilated and containing thrombi), mature adipose tissue, and smooth muscle bundles in variable proportions, identical to classic AML.

Half of the cutaneous AMLs are surrounded by a fibrous pseudocapsule, probably as a stromal response to tumor growth. Some cases present epidermal changes such as atrophy or hyperplasia. Faint chronic inflammatory infiltrate was also present in some cases [16,22].

Unlike classic AML, there is no epithelioid variant in cutaneous AMLs; consequently, they do not display cellular atypia, necrosis, or mitosis. Only one case had pleomorphic and bizarre nuclear changes in the smooth muscle component [13]; however, the absence of epithelioid cells, mitotic activity, necrosis, and the prolonged clinical duration (15 years) support the degenerative nature of these findings, similar to those observed in ancient schwannomas [13,121].

Special Stains

When requested, Masson's trichrome staining revealed smooth muscle cells in red and collagen fibers (present in the stroma and fibrous pseudocapsule) in blue. Elastic fiber staining shows an absent or defective lamina elastica in some vessels.

Immunohistochemistry

Cutaneous AML is characteristically positive for smooth muscle markers such as SMA, Calponin, and Desmin. However, unlike classic AML, all cutaneous AMLs are negative for melanocytic markers such as HMB-45, Melan-A, MART-1, and SOX-10. Other frequently positive markers include S-100, Factor VIII, CD31, CD34, and FLI1.

Treatment and Prognosis

Complete surgical excision is the diagnostic and therapeutic procedure indicated for cutaneous AML; these tumors are usually easily "shelled out" [11,12,23]. Cutaneous AMLs are always benign, do not progress, and only recur if excision is incomplete [17], highlighting the importance of complete removal with negative margins.

Differential Diagnosis

In the skin, some tumors are composed of one or more of the AML components. Angiolipoma is composed of mature fat cells and clusters of thin-walled capillaries and lacks smooth muscle bundles. Although angioleiomyoma is also characterized by thick-walled blood vessels (as in AML), its smooth muscle cells are arranged concentrically around blood vessels, and it lacks adipose tissue. Arteriovenous malformation is composed of large-caliber arteries, arterioles, capillaries, venules, and thick-walled veins; however, it lacks smooth muscle bundles and adipose tissue [1].

The most important differential diagnosis is classic AML in the skin [69] since they are histologically identical. The expression of melanocytic markers and distinct demographic/clinical features (previously described) are crucial for proper differentiation between these two entities.

Conclusions

Owing to the rarity of cutaneous AML, it is currently not included in the 2018 WHO classification of skin tumors [1]. Moreover, the current information still associates these tumors as cutaneous presentations of the classic AMLs with some differences.

Our review strongly suggests that cutaneous and classic AMLs must be considered separate entities. In summary, the main differences reside in the following aspects:

- Clinical: predominantly in males, more frequent in or around the ear, and presenting exclusively as a solitary lesion.
- Etiopathogenesis: without any reported association with TSC.
- Morphology: lacking aggressive variants such as EAML, necrosis, and atypical mitoses.
- Immunohistochemistry: absent melanocytic markers.
- Prognosis: benign behavior with lack of recurrence following complete surgical excision.

The immunohistochemical findings discard PECs or any other cell with melanocytic differentiation as a possible origin for cutaneous AML; hence, unlike classic AML, this tumor does not belong to the PEComa family. It is reasonable to consider cutaneous AML as a true and pure "angio-myo-lipoma."

Future updates of the WHO classification of skin tumors should consider including cutaneous AML as a separate entity. Finally, physicians should be aware of the possibility of a cutaneous AML when presented with a nodular mass in the ear, as appropriate treatment can provide patients with complete clinical resolution.

Conflicts of Interest

None declared.

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Abbreviations

- AML:** angiomyolipoma
- CT:** computed tomography
- EAML:** epithelioid angiomyolipoma
- MRI:** magnetic resonance imaging
- NF1:** neurofibromatosis type 1
- PEC:** perivascular epithelioid cell
- PEComa:** perivascular epithelioid cell tumor
- SMA:** smooth muscle actin
- TSC:** tuberous sclerosis complex
- WHO:** World Health Organization

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