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ORIGINAL ARTICLE

International Skin Imaging Collaboration-Designated Diagnoses (ISIC-DX): Consensus terminology for lesion diagnostic labeling

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Abstract

Background: A common terminology for diagnosis is critically important for clinical communication, education, research and artificial intelligence. Prevailing lexicons are limited in fully representing skin neoplasms.

Objectives: To achieve expert consensus on diagnostic terms for skin neoplasms and their hierarchical mapping.

Methods: Diagnostic terms were extracted from textbooks, publications and extant diagnostic codes. Terms were hierarchically mapped to super-categories (e.g. 'benign') and cellular/tissue-differentiation categories (e.g. 'melanocytic'), and appended with pertinent-modifiers and synonyms. These terms were evaluated using a modified-Delphi consensus approach. Experts from the International-Skin-Imaging-Collaboration (ISIC) were surveyed on agreement with terms and their hierarchical mapping; they could suggest modifying, deleting or adding terms. Consensus threshold was >75% for the initial rounds and >50% for the final round.

Results: Eighteen experts completed all Delphi rounds. Of 379 terms, 356 (94%) reached consensus in round one. Eleven of 226 (5%) benign-category terms, 6/140 (4%) malignant-category terms and 6/13 (46%) indeterminate-category terms did not reach initial agreement. Following three rounds, final consensus consisted of 362 terms mapped to 3 super-categories and 41 cellular/tissue-differentiation categories.

Conclusions: We have created, agreed upon, and made public a taxonomy for skin neoplasms and their hierarchical mapping. Further study will be needed to evaluate the utility and completeness of the lexicon.

INTRODUCTION

Clinical care requires clear communication between clinicians and pathologists about diagnostic categories that will guide management.[1] To be useful for educational, research and artificial intelligence (AI) training purposes, large skin imaging data sets need agreed-upon diagnostic labels with a clear-cut hierarchy.[2–8]

The International Skin Imaging Collaboration (ISIC) was established to facilitate use of skin imaging towards reducing mortality and morbidity from skin cancer.[8] A goal of ISIC is to standardize image acquisition, diagnostic labeling, metadata terminology and digital archiving towards

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development of a large image data set for educational and research purposes. Indeed, the ISIC image archive is a growing, open-source repository of skin neoplasms, available for teaching, conducting research and developing AI systems.[9] The ISIC archive has been the source of dermoscopic images for five international grand challenges leading to thousands of technical publications.[4,10,11] To date, ISIC has restricted itself to a dozen diagnostic categories of skin neoplasms. As ISIC archive broadens to represent the full gamut of skin proliferations, we find that prevailing dermatological lexicons are limited in their scope, consistency and granularity.

Herein, we focused on trying to achieve standardized diagnostic labeling of images of skin neoplasms based on correspondence with histopathological terminology. To this end, we have conducted a modified Delphi-consensus predicated on existing diagnostic lexicons and present the resulting taxonomy for broad international use.

MATERIALS AND METHODS

Consistent with previous studies, an institutional review board approval was not applicable to this study, as it included no research subjects[12]; all Delphi members were co-authors. Illustrative clinical images were retrospectively selected from an image database; written informed consent to publication of their case details was obtained from the patients whose images are depicted.

Study aims and initial development of diagnostic scheme

Our plan is to label existing and future ISIC-Archive images with diagnostic terms that most accurately and reproducibly represent the histopathological diagnoses. For each clinical-pathological entity, we sought the best diagnostic term, the pertinent modifiers and commonly used synonyms and the hierarchical mapping of diagnoses.

We began with several premises: (1) focus on neoplasms with few examples of inflammatory processes that may appear in the clinical differential diagnosis of skin lesions, and (2) convergence on agreed-upon diagnostic labels—prioritizing a unique ISIC-designated-diagnosis (ISIC-DX) term for each clinical-pathological entity.

Next, we extracted diagnostic terms from dermatopathology textbooks, scientific literature, online sources and extant diagnostic codes.[13–17] We created a three-tier hierarchy with the top level mapped to a 'benign' (Figure 1), 'malignant' (Figure 2) or 'indeterminate' (Figure 3) super-category.[18–20] Next, each diagnosis was mapped to cellular/tissue differentiation category; these categories were termed based on the cell type (e.g. 'melanocytic') or on the tissue element (e.g. 'vascular' or 'neural') from which the proliferation arises or with which it is closely associated. Synonyms were added to terms, to recognize variable diagnostic designations commonly used for the same entity. Finally, modifiers were defined as descriptors that allow further sub-categorization of terms, in a manner that is clinically or pathologically meaningful. For example, nevi are often sub-classified by pathologists as 'junctional', 'compound' or 'intradermal'.

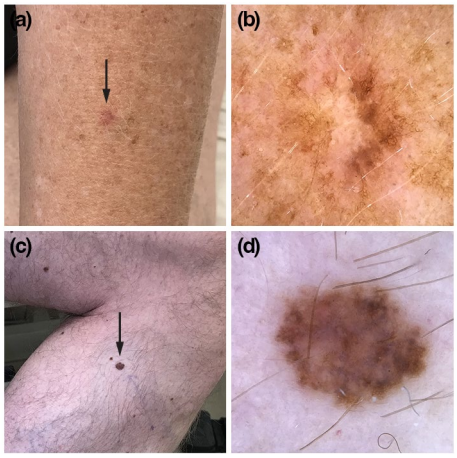

FIGURE 1 Examples of benign proliferations. (a) Clinical and (b) dermoscopic images of a lesion on the leg histopathologically diagnosed as 'dermatofibroma'. This lesion is classified into super-category 'Benign', cellular/tissue differentiation category. This lesion is classified into super-category 'Benign', cellular/tissue differentiation category 'Soft tissue proliferations – Fibro-histiocytic', diagnostic term 'Dermatofibroma, NOS. (c) Clinical and (d) dermoscopic images of a lesion on the leg histopathologically diagnosed as 'dysplastic compound nevus'. It is classified into super-category 'Benign', cellular/tissue differentiation category 'Melanocytic proliferations', diagnostic term 'Nevus, Atypical, NOS/Nevus, Dysplastic/Nevus, Clark', with modifier 'Compound'.

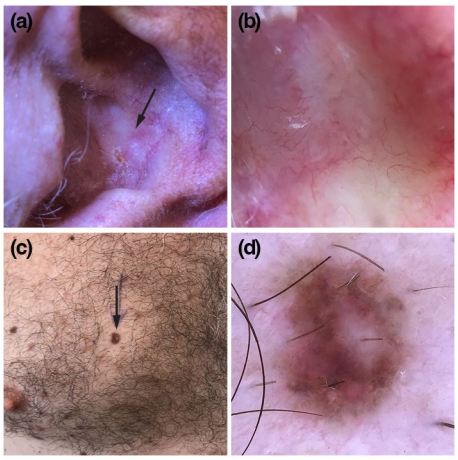

FIGURE 2 Examples of malignant proliferations. (a) Clinical and (b) dermoscopic images of a lesion on the ear concha histopathologically diagnosed as 'Basal cell carcinoma, sclerosing (morphea) type'. This lesion is classified into super-category 'Malignant', cellular/tissue differentiation category 'Adnexal epithelial proliferations – Follicular', diagnostic term 'Basal cell carcinoma, Sclerosing/morpheaform'. (c) Clinical and (d) dermoscopic images of a lesion on the chest histopathologically diagnosed as 'melanoma 0.5 mm in thickness, without ulceration, and with nevoid features'. It is classified into super-category 'Malignant', cellular/tissue differentiation category 'Melanocytic proliferations (melanoma)', diagnostic term 'Melanoma invasive, Nevoid', with modifiers 'Breslow depth 0.5 mm' and 'non-ulcerated'.

Delphi contributors and rounds

We utilized a modified Delphi method to attain consensus on the terminology lexicon.[21,22] We invited members of ISIC who are dermatologists and dermatopathologists to serve as Delphi experts by sending an email describing the study aims and Delphi methodology and asking recipients to preview the study user interface via a 6.5-min tutorial video.[23] Consent to serve as experts in the Delphi process was implied through self-registration and round completion.

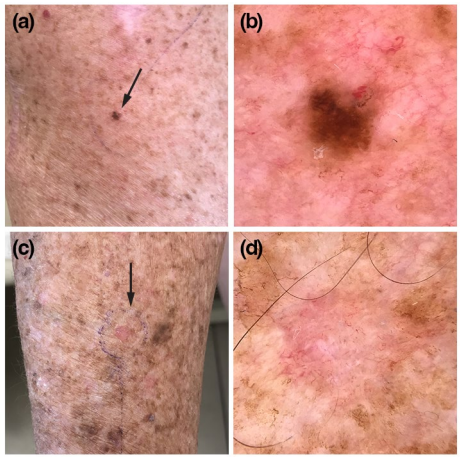

FIGURE 3 Examples of Indeterminate proliferations. (a) Clinical and (b) dermoscopic images of a lesion on the arm histopathologically diagnosed as 'atypical junctional melanocytic lesion, in favor of melanoma in-situ'. This lesion is classified as super-category 'Indeterminate', cellular/tissue differentiation category 'Melanocytic proliferations', diagnostic term 'Atypical melanocytic neoplasm' with modifiers 'Junctional', 'MPATH III' and 'Histopathological report favours melanoma'. (c) Clinical and (d) dermoscopic images of a lesion on the forearm, whereby the histopathological report described an 'atypical junctional melanocytic hyperplasia on sun-damaged skin, the possibility of a developing melanoma in situ cannot be excluded'. It is classified into super-category 'Indeterminate', cellular/tissue differentiation category 'Melanocytic proliferations', diagnostic term 'Atypical melanocytic neoplasm' with modifiers 'Junctional', 'MPATH III' and 'Histopathological report undecided'.

Contributors were surveyed on basic demographics and could recommend inclusion of additional experts as Delphi members. Contributors who completed all Delphi rounds were offered authorship in the ensuing publication.

In the first Delphi round, contributors were asked to review the entire list of ISIC-DX terms using a web interface (Figure 4). Contributors had to respond to each individual ISIC-DX term by marking the term as 'correct', denoting agreement with the term, its hierarchical mapping and when relevant, its synonyms and modifiers. Alternatively, they could select a modification: (1) suggest a different name for a term or category, (2) correct spelling of the term, (3) combine with another term, (4) assign term to another category in the hierarchical mapping, (5) edit synonyms or modifiers, (6) suggest additional synonyms or modifiers, (7) remove term entirely, (8) remove synonyms or modifiers, and (9) other free text suggestions. In addition, contributors could (1) suggest adding new categories in the hierarchical mapping, and (2) suggest adding new terms. At all times, they could refer to an overview of the entire taxonomy.

Results of the first round were evaluated after all experts submitted their surveys. Threshold for Delphi consensus was set at >75%.[24] A steering committee of three ISIC members (AS, VR and KL) who were not in the Delphi panel reviewed contributors' responses for terms that did not reach consensus and clustered these responses to multiple-choice items. In addition, the committee made majority-vote decisions on suggestions for added terms. These items formed the basis for the second Delphi round survey. Suggestions for new terms were not accepted after round one. At the second round, consensus threshold was retained at >75% for multiple-choice (>2) items, while threshold was set at a majority vote of >50% for items with only two choices. For items that did not reach consensus, we identified the top-two voted choices, for final evaluation at the third Delphi round. At the conclusion of the third round, threshold for consensus was set at a majority vote of >50%. For third round items with tied participant votes, the steering committee made a majority-vote decision. Delphi surveys and participants responses are available in a public repository.[25]

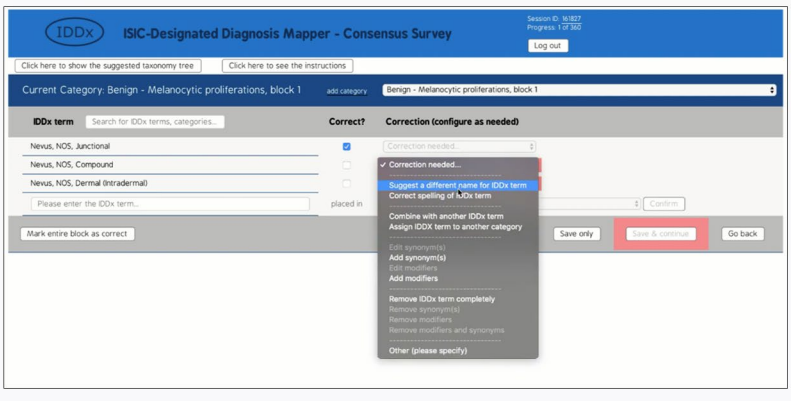

FIGURE 4 Screenshot of the web interface presented to members in the first Delphi round evaluation. In this exemplary page, Delphi members were presented with a batch of three ISIC-DX terms, Nevus, NOS-junctional, -compound and -dermal. The upper right box shows the hierarchical mapping of the terms to 'benign' super-category and 'melanocytic proliferations' category. Checking the 'correct?' box denoted agreement with the term. Alternatively, they could use a drop-down menu to suggest deleting or modifying the term or its associated mapping.

Statistical design

Descriptive and relative frequencies were used to describe the survey respondents and the results of the consensus. Measures of central tendency were calculated. Agreement threshold >75% for 18 Delphi members was calculated as ≥14 consensus votes and >50% as ≥10 votes.

RESULTS

Delphi contributors

Invitations to contribute to the study were sent to 36 clinicians. Of 36 invited, 18 (50%) completed all Delphi rounds (10 dermatologists, four dermato-pathologists and four with a dual certification); five (14%) initially agreed to be Delphi members, but did not complete round I; three (8%) declined and 10 (28%) did not respond.

Round I

Round I was held between November 2019 and January 2020. Overall, there were 379 ISIC-DX terms (benign = 226, malignant = 140 and indeterminate = 13). Of 379 terms, 356 (94%) passed the 75% threshold in round I. Twenty-three terms, including 11/226 (5%) benign-category terms, 6/140 (4%) malignant-category terms and 6/13 (46%) indeterminate-category terms, did not reach agreement. These were carried over to round II as 34 items, including ISIC-DX terms ($n = 16$), modifiers ($n = 7$), synonyms ($n = 8$), assignment of terms to another category in the hierarchical mapping ($n = 2$) and change of cellular/tissue differentiation category name in the hierarchical mapping ($n = 1$). In addition, 29 newly suggested terms were introduced into round II.

Based on the contributor feedback, the steering committee decided to remove the inflammatory ($n = 15$) and infectious terms ($n = 12$) and focus solely on skin neoplasms. This reduced the total number of approved ISIC-DX terms, at the conclusion of round I, from 356 to 329 terms.

Round II

Round II was held from August to October 2020. Contributors voted on 63 items carried over from round I. Of 34 items related to existing terms, 22 items (65%) surpassed the agreement threshold, including 6/16 (38%) terms, 7/7 (100%) modifiers, 7/8 (88%) synonyms, 1/2 (50%) for assignment of

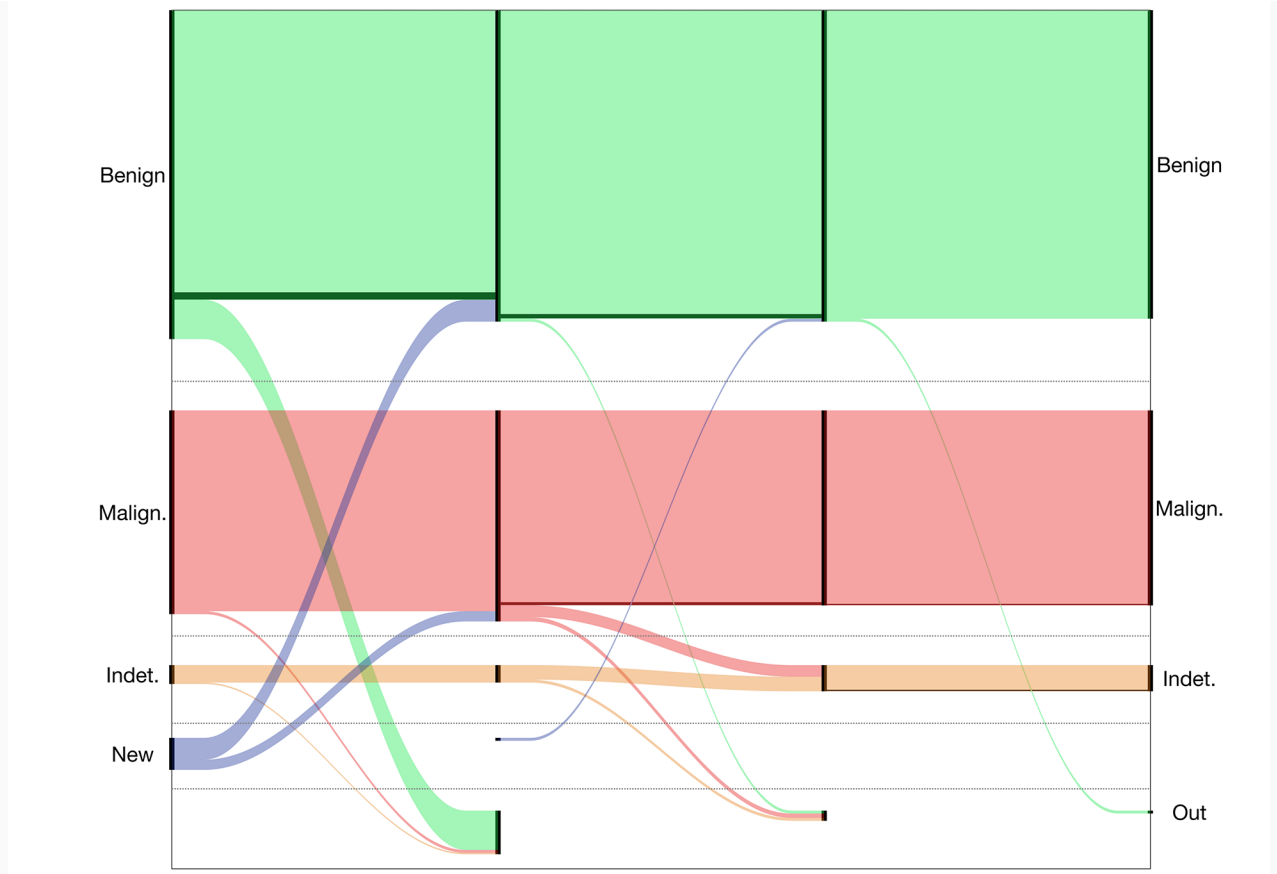

FIGURE 5 Alluvial plot depicting the amendments made in the ISIC-DX taxonomy across the three rounds of Delphi. For example, the green thick curved line shows the fraction of terms from the benign super-category that were eliminated after round I. The two purple thick curved lines on the left shows new terms introduced into the benign (top line) and malignant (bottom line) super-categories following round I.

terms to another category in the hierarchical mapping and 1/1 (100%) for change of cellular/tissue differentiation category name in the hierarchical mapping—under 'benign' super-category, 'deposits' was renamed 'exogenous'. In addition, 26 of the 29 (90%) new terms introduced in round II exceeded the agreement threshold. Fourteen multiple-choice items did not reach the agreement threshold; the two terms with the highest number of votes for each item were carried over to Delphi round III. Finally, one binary-choice item—should 'solar lentigo' be categorized under 'flat melanotic pigmentations' or under 'epidermal proliferations'—had a tie of votes (9/18 for each option); the steering committee made a majority vote to retain the original classification of 'solar lentigo' under 'epidermal proliferations', even though some solar lentigines exhibit a measure of melanocytic hyperplasia.

Round III

Round III was held between February and April 2021. Contributors voted on 14 entities from round II, including existing terms ($n = 10$), newly suggested terms ($n = 2$), synonyms ($n = 1$) and assignment of terms to a category ($n = 1$). Of these, 13 items (93%) reached consensus by majority vote. There was one item—whether to combine 'Nevus, Atypical, NOS', 'Nevus, Dysplastic' and 'Nevus, Clark' into one ISIC-DX, or to Combine 'Nevus, Atypical, NOS' and 'Nevus, Dysplastic', while deleting 'Nevus, Clark'—that did not reach consensus because of a tied vote. The steering committee made a majority vote for the former option of combining all three into one term, namely 'Nevus, Atypical, NOS/Nevus, Dysplastic/Nevus, Clark', classified under 'benign' 'melanocytic proliferations'.

In addition, the steering committee added two survey items to maintain consistency of the terminology. First, contributors decided in round II to move the term 'solar (actinic) cheilitis' from 'malignant' to 'indeterminate' super-category. In round III, they were surveyed and confirmed that all 'solar keratosis' terms be moved from 'malignant' to 'indeterminate' super-category, under 'epidermal proliferations'. Second, contributors decided in round II to delete the term 'PUVA keratoses'. In round III, they were asked whether the term 'arsenical keratoses' should be deleted as well and voted in favour of deletion of this term.

An overview of the amendments made in the ISIC-DX taxonomy across the three rounds of Delphi is depicted (Figure 5). The final consensus list consists of 362 ISIC-DX terms (Appendix S1). The 'benign' super-category encompasses 20 categories and 210 terms (Figures 1 and 6); the

FIGURE 6 Overview of the categories and terms under the 'benign' super-category.

'malignant' super-category—19 categories and 134 terms (Figures 2 and 7); and the 'indeterminate' super-category—2 categories, namely 'melanocytic proliferations' and 'epidermal proliferations', and 18 terms (Figures 3 and 7).

DISCUSSION

Herein, we present a Delphi-based, proposed clinical-pathological categorization of skin neoplasms. We share our initial attempt to develop a consensus lexicon designed for use as diagnostic labels for improved clinician communication, education, research and AI training. We also plan to apply this terminology for labeling of the images used in the ISIC Archive.

Our initial strategy was to adopt an existing authoritative taxonomy, however, we found them lacking in scope, granularity and consistency. There have been efforts to standardize diagnostic terminology, including ICD10[26] and SNOMED.[27] Yet, the clinical utility and reproducibility of terms used by these coding systems have been previously called into question.[28–30] For example, among benign melanocytic proliferations, the current Delphi consensus recorded 36 ISIC-DX terms; of these, 26 would not have a distinctive ICD-10 diagnosis, which could detract from the clarity of diagnostic labeling of the ISIC archive. To fill some of these gaps, pathologists have suggested additional structured reporting schemes, such as the MPATH-Dx and the codes of the College of American Pathologists.[1,31] Indeed, MPATH-Dx provides an encompassing scheme for structured labeling of melanocytic proliferations with associated treatment recommendations.[32-34]

Ideally, all neoplasms could be categorized into benign versus malignant super-categories. In reality, as highlighted by MPATH-Dx, there are many examples of lesions (e.g. 'Atypical Intraepithelial Melanocytic Proliferation') for which their malignant versus benign status is debated. However, exclusion of such relevant 'borderline' cases from clinical training and education and from AI training risks undermining the diagnostic accuracy of clinicians in daily practice, as well as that of AI systems. Hence, we added an 'indeterminate' super-category to the first tier of our hierarchical scheme. Almost half (46%) of the ISIC-DX terms under the 'indeterminate' super-category did not reach consensus in the first round of the Delphi, while about 95% of the terms under 'benign' and 'malignant' super-categories did. This likely reflects clinicians' ambiguous view of entities whose biological behaviour is still deliberated. While the 'indeterminate' super-category initially only included the category 'melanocytic proliferations', the consensus panel decided to include all terms related to 'solar (actinic) keratosis' under 'indeterminate' 'epidermal proliferations'. This categorization echoes an old literature deliberation on the nature of solar keratosis.[35–37] However,

FIGURE 7 Overview of the categories and terms under the 'malignant' (red) and 'indeterminate' (brown) super-categories.

inclusion of an entity in the 'indeterminate' category does not imply that these lesions have biological malignant potential, but rather difficulty in placing an entity into benign or malignant category.

The terms 'dysplastic nevus' and 'atypical nevus', whose definitions are varied,[38–42] did not reach consensus by the experts following three Delphi rounds. In the first round 'dysplastic nevus', 'atypical nevus' and 'Clark nevus' were presented as three distinct terms under 'benign' 'melanocytic proliferations'; none surpassed the 75% threshold. Even in round III, the top two options—combine all three terms versus combine only 'atypical nevus' and 'dysplastic nevus'—received a tied vote. Finally, the steering committee, using a simple-majority vote, chose the more inclusive option of combining all three diagnoses to one ISIC-DX term 'Nevus, Atypical, NOS/Nevus, Dysplastic/Nevus, Clark'. This was thought to be the best approach given the overlapping use of the terms in labeling subsets of nevi, while being cognizant that these terms are not strict synonyms.

The proposed lexicon has limitations. First, we chose to restrict the scope of diagnostic terms for practicability. Future efforts may need to specifically enrich image data sets for rare diagnoses, and expand the taxonomy to include inflammatory or infectious disorders. Second, we chose to limit granularity for each diagnosis. While ancillary immunohistochemical and molecular markers may gain importance in distinguishing variants of diagnoses, Delphi members focused on the current clinical relevance of diagnostic entities. Eventually, we anticipate that a more molecularly informed ontology of diagnoses will lead to improved diagnostics labels. Lastly, the lexicon has not been tested prospectively. To understand the completeness, applicability and reproducibility of the taxonomy, we plan to study the prospective labeling of images submitted to the ISIC archive. We anticipate that the terms may need to be periodically updated.

In conclusion, we propose a publicly available, expert consensus-based taxonomy for diagnostic labeling of images of skin neoplasms. The ISIC-DX lexicon may benefit clinical communication, teaching and research and may improve AI training and interpretability. Further study and feedback from the dermatology community will be needed to evaluate the utility and the completeness of the lexicon.

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CONFLICT OF INTEREST STATEMENT

A Scope—Consulting fees (stated as not relevant for this publication) from Roche Pharmaceuticals (Israel) LTD; Payment or honoraria for lectures, presentations, speakers bureaus, article writing or educational events (stated as not relevant for this publication) from Janssen Israel. RP Braun—Advisory board (stated as not relevant for this publication) from Allmiral. MA Marchetti—Grants from Harry J. Lloyd Charitable Trust—Funding to institution for study unrelated to this work; Payment or honoraria for lectures, presentations, speakers bureaus, article writing or educational events from American Dermoscopy Meeting and Medscape. AA Marghoob—Royalties or licences from Up To Date and Informa publishing; Payment or honoraria for lectures, presentations, speakers bureaus, article writing or educational events from DermLite and FotoFinder; Receipt of equipment, materials, drugs, medical writing, gifts or other services from Heine, DermLite and FotoFinder. HP Soyer—Consulting fees (to institution) from Canfield Scientific Inc, MoleMap Australia Pty Ltd and Blaze Biosciences Inc; Patents planned, issued or pending for Microbiopsy Device; Stock or stock options—Shareholder MoleMap NZ Limited and Shareholder e-dermconsult GmbH. A Stratigos—Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, made to institution, from BMS, Janssen Cilag, Sanofi, Genesis Pharma and Regeneron. L Thomas—Receipt of equipment, materials, drugs, medical writing, gifts or other services, made to institution, from Casio, 3 GEN, Heine, Fotofinder and C-Cube. H Kittler—Royalties or licences from Casio, Heine.

Meta-Optima, Barco; Payment or honoraria for lectures, presentations, speakers bureaus, article writing or educational events from Fotofinder, Heine, Almirall, Novartis, Pelpharam and Eli Lilly; Participation on a Data Safety Monitoring Board or Advisory Board for La Roche Posay. V Rotemberg—Grants—KL2 award to Dr. Rotemberg from NIH NCATS. AC Halpern—Consulting fees from Canfield Scientific Inc. and SciBase; stock or stock options from Mutual Funds. All the other authors, including K Liopyris, J Weber, RL Barnhill, CN Curiel-Lewandrowski, DE Elder, G Ferrara, JM Grant-Kels, T Jeunon, A Lallas, JY Lin, C Navarrete-Dechent and G Pellacani have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available at https://github.com/neuroelf/dermodelphi.

ETHICAL APPROVAL

Consistent with previous studies, an institutional review board approval was not applicable to this study, as it included no research subjects; all Delphi members were co-authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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