

The deep imaging phenotype for melanoma risk stratification

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Abstract

Targeted surveillance for individuals at high-risk for melanoma is increasingly recognized as a feasible and effective alternative to population-wide melanoma screening. However, current risk stratification models to identify these high-risk individuals are often reliant on subjective or self-reported metrics, which are vulnerable to bias and poor reproducibility. The deep imaging phenotype describes the concept of leveraging parallel advances in total body photography (TBP) and artificial intelligence (AI) to improve risk stratification using personalized severity and spatial distribution of cutaneous risk factors. This narrative review explores the progress towards the deep imaging phenotype in dermatology, with a focus on its clinical applications, challenges, and future directions. It explores (i) the limitations of existing melanoma risk prediction, (ii) advancements in TBP and AI-driven analysis of the cutaneous phenotype; (iii) integration of phenotype with clinical and genomic information; (iv) frameworks for clinical, logistic, and ethical implementation of phenotypic measures into clinical practice. Progress towards the deep imaging phenotype has included algorithms that report nevus characteristics (count, size, and distribution), severity and distribution of photodamage, facultative and innate skin tones, freckling, and other parameters for objective and personalized risk stratification. Phenotypic measures correlate with melanoma risk and may be integrated with traditional clinical and genomic risk factors to enhance current risk assessment. Clinicians and consumers report acceptance of this approach, although, most evidence to date focuses on individual phenotypic features rather than the collective synergy of all measures. Supporting information technology infrastructure, legal frameworks, and clinical guidelines are underdeveloped and should be prioritized before clinical implementation. Objective risk stratification using personalized cutaneous risk factors may empower the effective allocation of resources, reduce over-surveillance in low-risk populations, and offer timely interventions to individuals at high risk.

Key words: Melanoma, AI, Artificial Intelligence, total body photography, risk prediction, skin cancer



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1. Introduction

Melanoma is a significant global public health challenge, with age-standardized incidence rates reaching 23 per 100,000 persons in Europe, 32 in the United States, and 54 in Australia. The clinical paradigm of early detection aims to identify high-risk, early-stage melanomas for surgical excision prior to the progression to metastasis, and aims to reduce morbidity, and mortality [1, 2]. However, a growing consensus identifies that many excisions represent low-risk melanomas that have negligible potential for harm within the patient's lifespan [3]. The detection of indolent lesions resembling melanoma, described as overdiagnosis, is a major limitation to the efficacy and cost-effectiveness of population-wide screening for melanoma [4]. Instead, increasing evidence supports the role of targeted surveillance of specific individuals likely to develop a high-risk melanoma capable of metastasis [5, 6]. Targeted screening aims to address the parallel dilemma of early detection and overdiagnosis by focusing surveillance towards individuals most likely to develop melanoma.

Accurate assessment of melanoma risk is highly reliant on contextualization through the clinical phenotype. Specifically, dermoscopy allows for the scrutiny of specific lesions for morphology that is correlated with the risk of metastasis. This dermoscopic information is integrated within an individual's clinical phenotype, consisting of established and visual risk factors, to understand the holistic likelihood of melanoma [7]. Clinical risk factors include age, sex, pigmentation traits for the hair, eyes, and skin, the number of blistering sunburns, nevi characteristics, and history of prior melanoma [8]. Considerable interest has been focused towards methods to reliably measure clinical risk factors to integrate into risk prediction tools for melanoma, and inform clinical and skin self-examination recommendations [5]. Current validated risk stratification tools have been designed to predict risk for the next three to twenty years, usually achieving sensitivity and specificity of approximately 30 and 80 percent, respectively [9, 10]. Modelling of risk-stratified targeted surveillance demonstrated a likely reduction in unnecessary medical interventions [10]. However, considerable controversy remains both over the absolute risk that necessitates regular surveillance, and recommendations for individuals who require reduced surveillance.

A number of melanoma risk stratification tools have been developed to date but none have been systematically implemented into clinical practice. A major barrier to clinical implementation is an overreliance on subjective measures prone to invalidating bias, as was identified by a recent systematic review of risk prediction models [8]. Addressing this bias by developing objective and reproducible methods may improve predictive accuracy, clinician uptake, and consumer trust. For example, nevus count is amongst the strongest risk factors for melanoma incidence, however often relies on self-reported counts and/or pictorial scales, that are prone to bias and poorly correlate with true nevus counts [11]. Furthermore, neither of the 40 existing prediction models reviewed considered large (>5 mm) nevus count, which strongly correlates to dysplastic nevus syndrome and melanoma risk [8]. Next, ultraviolet exposure, which is the leading environmental risk factor attributed to melanoma incidence, is often captured using subjective assessment of photodamage or surrogate outcomes, which has only a modest correlation to melanoma [12, 13]. These clinical metrics include self-reported sun exposure, number of sunburns, and outdoor leisure activities

that are prone to recall bias, socially-desirable answers, and fail to capture the complexities that define the mutation burden incurred within the epidermis [8]. For these phenotypic risk factors, an individual's skin topography may provide quantifiable and objective evidence to personalize risk assessment [7].

Parallel advances in skin imaging technology and artificial intelligence (AI)-driven image analysis presents new opportunities to enhance traditional risk stratification based on an individual's unique skin characteristics. This concept is described as the deep imaging phenotype, based on data obtained through total-body photography (TBP), dermoscopy, and questionnaires, analyzed using AI models to extract severity and spatial distribution of personalized risk factors for melanoma, including nevus pattern characteristics, photodamage, skin tone, and freckling [7]. The rationale for this approach is derived from population-based studies that demonstrate a high variability in the severity and distribution of phenotypic risk factors both across body sites of a single individual, and between individuals within a population [14, 15]. Integrating the personalized deep imaging phenotyping with traditional risk factors such as age, sex, personal and family history for melanoma may facilitate more nuanced risk stratification. From an individual standpoint, a holistic whole-of-person approach may contextualize a suspicious lesion with the surrounding skin phenotype and individual risk for malignancy [16]. Across the broader population, deep phenotyping may assist to tailor screening recommendations, target interventions, and improve resource allocation to individuals most likely to develop a high-risk melanoma [5]. Figure 1 illustrates a conceptualization of key features described using the deep imaging phenotype.

This narrative review explores the progress of deep image phenotyping in dermatology, with a focus on its clinical applications, challenges, and future directions.

2. The deep imaging phenotype

2.1. Nevi

Greater nevus counts are amongst the strongest risk factors for cutaneous melanoma. The biological basis for the association between nevi and melanoma is through an increased genetic propensity for melanocyte proliferation that leads to the development of nevi, and in a subset of individuals a melanoma diagnosis [17]. This phenomenon is described as a specific pathway to melanoma development, where individuals with a high nevus count and genetic propensity for melanocyte proliferation may develop a melanoma even without excessive ultraviolet exposure [17]. Nevus counts are typically recorded as total counts of pigmented lesions greater than 2 mm in diameter, or large nevi greater than 5 mm, which are in turn more likely to be dysplastic. Meta-analysis has identified that a total body nevus count greater than 15 increases the risk for a first melanoma by 1.4-fold, and a nevus count above 100 by 4.6-fold [18]. The presence of large (>5 mm) or dysplastic nevi are independent risk factors from total nevus count and are associated with increased risk of melanoma of 1.6-fold for a single dysplastic nevus to 10.5-fold for five or more dysplastic nevi [18]. Meta-analysis report similar findings for the incidence of subsequent primary melanoma, where more than 15 total nevi increased risk by 1.6-fold and at least one dysplastic nevus is associated with a 3-fold risk increase [13]. Total

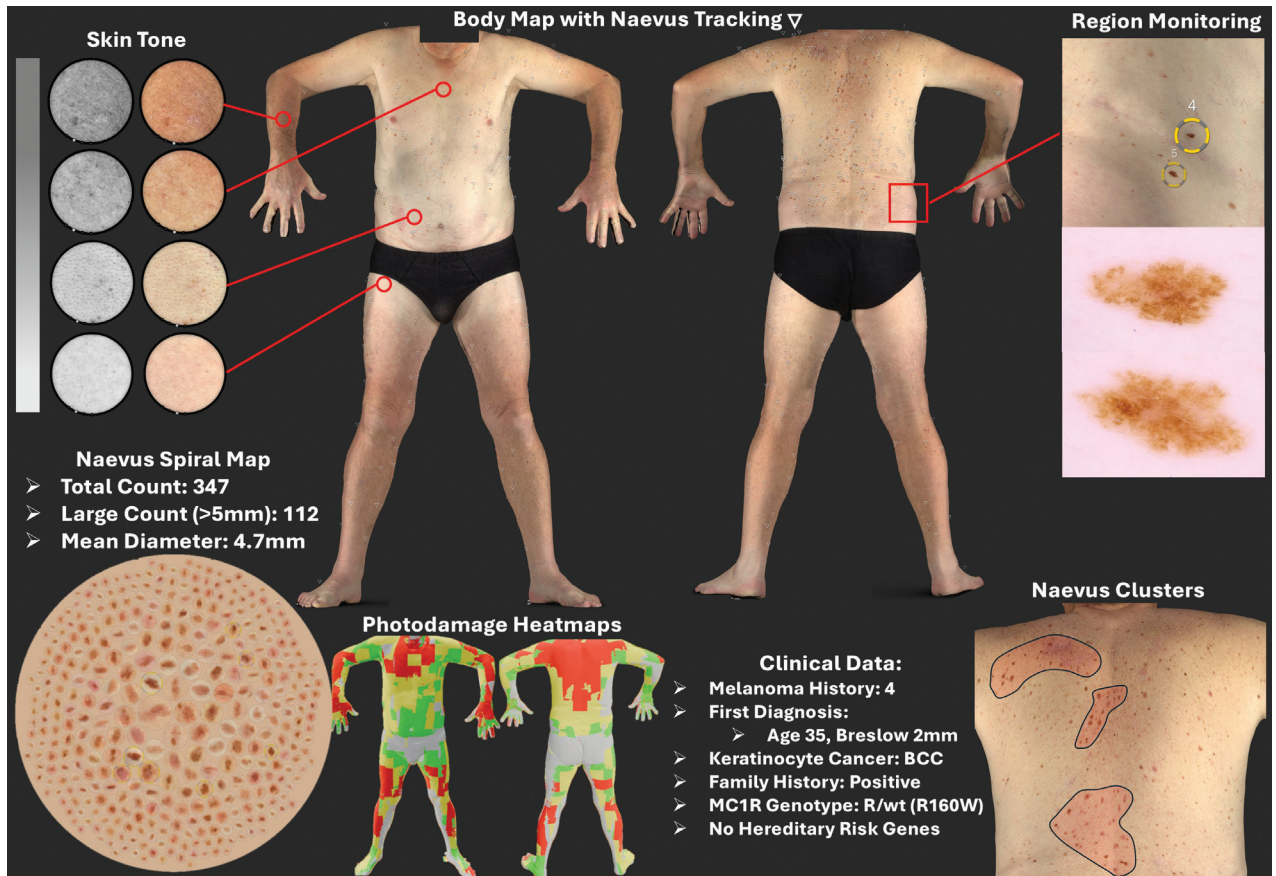


Figure 1. Deep imaging phenotype conceptualized with a 3D-TBP personalized avatar, integrated with (left to right): Site-specific skin tone; Nevus spiral map to visualize nevus count, size, and morphology; Body map with nevus tracking; Photodamage heatmaps mapping areas of mild (green), moderate (yellow), and severe (red) photodamage; Clinical information including genomics; Nevus spatial analysis identifying areas of clustered naevi compared to random or dispersed patterns; High-risk body region monitoring to detect local recurrence (scar) and adjacent sequential dermoscopy.

and large nevus counts were the strongest risk factors for a subsequent primary melanoma second only to a pathogenic variant at the *CDKN2A* locus [13].

Reproducible assessment of nevus counts has been a significant barrier to its implementation in melanoma risk assessment. Traditionally, nevus counts were collected through manual clinician counts from either in-person examinations or from TBP. This process is however, time consuming, subjective, and achieves poor reproducibility even when completed by experienced dermatologists [19]. Efforts to simplify nevus counting have utilized patient self-report at a single body site assisted by visual pictorial scales, which similarly has poor agreement, and assumes that a single body region can be extrapolated to the entire body surface area [11].

To address the limitations of manual nevus counting, Betz-Stablein et al. developed an AI algorithm to accurately report the total and large nevus count directly from TBP [20]. The distinct pigmentation changes between a nevus and its surrounding skin are highly amenable to automatic counting by AI. The algorithm performed strongly with sensitivity and specificity of 0.79 and 0.91 for all nevi, and 0.84 and 0.91 for nevi greater than 5 mm. A limitation of the algorithm is the capacity to distinguish nevi from lentiginos or flat seborrheic keratoses arising on photodamaged skin, although, the macroscopic and der-

matoscopic morphology between these lesion types is often indistinguishable even for experienced clinicians. Therefore, clinicians should exercise caution when interpreting AI-derived counts in individuals with a high count of seborrheic keratoses relative to true nevi. Non-nevi keratinocyte and inflammatory lesions were effectively excluded using a confidence threshold of 80% nevus likelihood. A major strength of the algorithm is that it has been integrated with one 3D-TBP software, where it allows instantaneous point-of-care reporting of nevus counts. The integrated software tags the location of each nevus on personalized patient avatars to facilitate clinical interpretation, tracking of new and existing nevi across serial imaging, and allowing human-in-loop verification of automated nevus counts [16].

Emerging evidence supports that the distribution of nevi across the body surface area may help further assess melanoma risk. The hypothesis of spatial randomness posits that the anatomical distance between adjacent pigmented lesions may differ between melanoma and nevi. Two studies have conducted patient and lesion-level spatial analyses from 3D-TBP and observed whether the spatial distribution was clustered, random, or dispersed. Individuals at high-risk for melanoma were more likely to have a clustered distribution [21], and for individuals at low-risk for melanoma, a dispersed distribution was more likely [22]. In both risk cohorts, individuals with a clustered distribution had a two-fold greater likelihood that a melanoma would arise within close proximity to adjacent pigmented lesions. The most plausible biological hypothesis to support the spatial randomness is a non-random distribution of genetically distinct melanocyte subpopulations [21]. Many pigmentation skin conditions appear with a mosaic pattern, pointing to a causal genetic alteration during embryogenesis, prior to maturation and migration into the final adult cutaneous distribution. Mosaic subpopulations may be affected in a special way throughout adulthood by external stimuli including ultraviolet exposure [14]. Supportive of this, alleles associated with nevocarcinogenesis are described to present in mosaic distributions throughout the epidermis, including mutated BRAF and NRAS genes [23]. Validation of the spatial randomness hypothesis may define protocols for implementation in 3D-TBP-derived risk stratification.

2.2. Photodamage

Ultraviolet exposure is the primary environmental risk factor for melanoma. Melanocytes exposed to chronic or intermittent sunlight incur a disproportional burden of mutations compared to non-exposed melanocytes. Phenotypic visual photodamage is the strongest correlate to the mutational burden, exceeding even histopathologic markers of photodamage including elastosis and epidermal thinning [24]. However, the challenge for accuracy and time-effective measurement results in photodamage being rarely considered for risk stratification [8]. Models that consider photodamage typically measure and extrapolate from a single site (i.e. upper back) [8], which fails to capture the high variability in distribution and severity that exists both between individuals, and across body sites in the same individual [14]. Consistent with this, existing photometric scales to assist in the assessment of photodamage are limited to the upper back, forearm, and face [25–27]. The complexity of cutaneous photodamage would benefit from a detailed and site-specific assessment that acknowledges the variation in anatomical distributions.

Convolutional neural networks (CNNs) represent a machine learning-based model that can be used to objectively quantify phenotypic photodamage. Creating image-based datasets for dermatology image classification represents a challenging task due to the variability in appearance of the skin surface [28]. Whilst distinct cutoffs such as mild or moderate appearance are required to facilitate clinical interpretation, these artificial cutoffs introduce ambiguity given that photodamage exists on a continuum without definitive setpoints between severity classes. To address this ambiguity, our center employed a multi-task machine learning strategy that considers pigmentation as a co-variate to increase the prediction accuracy for photodamage. The development pipeline included the creation of a photometric scale to facilitate reproducible annotation of photodamage and pigmentation across all body sites from 3D-TBP. The objectivity of this scale was validated by strong agreement between dermatology researchers and laypeople without dermatology experience. Annotated images were used to train a CNN with a high 94% accuracy in classifying photodamage compared to human readers. Compared to a CNN without pigmentation, the multi-task learning method to include pigmentation significantly improved the model's capacity to distinguish mild and severe photodamage from moderate. A strength of this model is the overlay of photodamage assessment as heatmaps over personalized patient avatars to aid in explainable output, clinical assessment, and patient understanding. It is anticipated that the level of photodamage will assist in risk stratification specific to chronic sun damage-related melanoma arising from middle age and onwards.

2.3. Skin tone

Skin tone is a well-established risk factor for ultraviolet sensitivity and therefore cutaneous malignancy. The clinical estimation of skin tone reflects the variable quantity of chromophores that absorb light within the visible spectrum, including: black-brown eumelanin, red-yellow pheomelanin, red hemoglobin, red-yellow carotene, and other minor components [29]. The dominant chromophore is eumelanin which is produced by melanocytes, and distributed to surrounding keratinocytes, where it forms a protective cap-like structure around the nucleus to scatter ultraviolet light and prevent nuclear DNA and RNA damage [30, 31]. A darker skin tone is therefore a visible biomarker that describes the genetic capacity for melanocytes to produce melanin and protect the epidermis from ultraviolet tumorigenesis. Individuals with a darker skin tone are less likely to be affected by melanoma or keratinocyte malignancies [29].

The Fitzpatrick Skin Type is currently the most common clinical tool used to estimate skin tone and skin cancer risk. The tool was first designed to estimate the sensitivity of light skin types (I–IV) to ultraviolet A (UVA) exposure to guide psoralen-UVA therapy [32]. Two further brown and dark (V and VI) tones were retrospectively added to expand the use of this scale to describe tone in a broader population, however it still falls short of capturing darker skin tones adequately [33]. Currently the Fitzpatrick Skin Type is an amalgamation of skin tone, propensity to sunburn, and other pigmentation traits such as eye and hair color (at age 21), used to describe an overall pigmentation phenotype. The Fitzpatrick scale is reproducible when applied by dermatologists, but has low

reproducibility using patient self-report, and lacks accuracy to differentiate skin of color [34]. Several scales have addressed inclusivity of all skin tones, such as the Monk scale that expands Fitzpatrick types V–VI into four categories [35]. The Eumelanin Scale further aimed to introduce objectivity through direct measurement of cutaneous melanin and erythema between wavelengths 400–700 nm, although requires specialist equipment, and has not been validated to correlate to the mutational burden incurred by ultraviolet exposure [36, 37].

The Individual Typology Angle (ITA) was devised as an objective and inclusive scale for broad application in dermatology. The ITA is based on the colorimetric system of the Commission Internationale de L'Eclairage (CIE) that quantifies color to the degree of grey between a range of black and white (Luminescence), a red-green component (a^*), and a yellow-blue component (b^*), all derived from a colorimeter device [37, 38]. From these, the luminescence and yellow components are used to quantify skin tone that can be interpreted as a continuous scale or categories ranging from very light to dark [38]. The ITA is highly correlated to the biologically efficient dose (BED) of ultraviolet light required for sunburn and the number of histologic sunburn cells [29]. Within melanocytes, ITA was highly correlated to a dose-dependent increase in ultraviolet-related DNA lesions across skin types from very light to tan [29]. Notably, brown-dark skin was largely resistant to melanocyte DNA damage, relevant to the epidemiology of both melanoma and pigmentary disorders [29]. However, clinical implementation of the ITA is limited by the requirement for specialist equipment, and guidelines to select a representative field of skin for tone analysis.

3D-TBP presents the opportunity to capture whole-of-body skin tone as an objective risk factor for skin cancer. Specifically, TBP images contain the constituent color data that can be extracted to calculate the site-specific ITA [16]. This whole-of-body approach circumvents the bias introduced by the subjective Fitzpatrick scale, or inaccuracies of measuring a single site with a colorimeter [7]. The innate skin tone at unexposed body sites (i.e. buttock, inner arm) informs the skin tone, which is in turn highly correlated to the incidence of cutaneous malignancies including melanoma [29]. The innate tone can be compared to the severity and distribution of the facultative skin tone at sun-exposed body sites (i.e. forearm) to estimate solar exposure and the capacity to tan [7]. Challenges to developing an AI that automates analysis of skin tone include the exclusion of non-target pigmented structures such as hair, and interpretation of the mottled and highly variable tones that occur in poikilodermatous photodamaged skin. Given that the ITA is highly correlated to the mutational burden of keratinocytes and melanocytes, it is anticipated that automated skin tone will enhance risk stratification with peri-lesional area, body region, and detailed inter-individual data.

2.4. Freckling

Ephelides, commonly known as freckles, emerge early in life and therefore may be an effective risk factor for younger individuals under the age of 40 years. Ephelides arise after intensive solar exposure in the childhood of genetically predisposed individuals, such as carriers of a Melanocortin 1 Receptor Red Hair Color (*MC1R*-RHC) allele, and fade with age and in winter. Self-reported ephelides are commonly included in risk stratification models given that their

presence is largely independent of other risk factors such as nevus counts and skin tone [39]. Freckles are commonly included as present or absent on the face, although, evidence points to a two-fold increase in melanoma risk for freckling presence on either the face or iris [18, 40]. To make the assessment more objective, a photonumeric scale has been developed for reproducible grading of freckling from absent to severe from the face, chest, and upper arms using 3D-TBP [41]. It is anticipated that this photonumeric scale can be used to facilitate machine learning for developing automated algorithms to report freckling as a risk factor for melanoma.

2.5. Anthropomorphic measures

The International Agency for Research on Cancer has called for broad research into melanoma risk factors [42]. Recent cohort and population-level analyses have proposed a correlation between melanoma risk, BMI [43], height and body surface area [44]. Thus far, a study has demonstrated that height and BMI can be extracted from 3D-TBP with similar accuracy to purpose-built laser body scanners to facilitate automated collection from existing clinical infrastructure [45]. It is likely that other algorithms will soon be developed to opportunistically report health-related anthropomorphic measurements including waist circumference, body composition, and assessment of android or gynoid structure.

2.6. Genetic data integration

Personalized genomics may capture intrinsic melanoma risk that cannot be captured in a quantifiable cutaneous phenotype. Evidence points to a strong genetic basis for melanoma with heritability estimated to be 58% from the largest relevant twin study that included 2766 monozygotic and 2866 dizygotic twins [46]. Current genetic testing aims to detect moderate-high penetrance genes that account for strong family history of melanoma in less than 1% of the population, including *CDKN2A*, *BAP1*, *POT1*, *POLE*, *TERT*, and *MITF* [47]. However, outside of familial cases, this heritable risk is largely attributed to the cumulative incidence of low penetrance (<10%) alleles that are carried at high frequencies (>0.1%) across the general population [48]. The latest genome-wide association study meta-analysis identified 54 loci significant for melanoma risk and related traits including nevus count, pigmentation traits, and telomere maintenance [48]. When combined within a polygenic risk score (PRS), these loci capture 30% of heritable risk, from which 25% is attributed to *MC1R*-RHC alone [49]. Central to the argument for genetic testing, carriers of *MC1R*-RHC variants have a two-fold increased melanoma risk for each *MC1R* allele, regardless of whether the high-risk pigmentation phenotype is visually apparent [49]. Genetic mapping within the UK has surprisingly revealed that individuals with two high-risk *MC1R*-RHC alleles are more likely to have blonde or light brown hair, compared to red [50]. Incorporating the PRS has been previously demonstrated to improve the discriminative capacity of existing risk stratification tools [51], although, validation at a larger scale is required to define the specific individuals that may benefit from genetic risk stratification.

3. Real world applications

3.1. Targeted screening

Emerging evidence supports an approach for targeted melanoma surveillance for individuals considered to be at high risk [3, 5]. Targeted screening aims to address the parallel dilemma of over and under-diagnosis, that is defined as detecting a high number slow-growing indolent lesions that are unlikely to cause harm in a low-risk patient's lifetime, whilst failing to achieve early detection of rapid-growing lesions that contribute to morbidity and mortality in a high-risk patient [52]. However, controversy exists on the definition of high risk. The US Preventative Task Force has implied that individuals with a personal history of a melanocytic or keratinocyte cancer constitute as high risk [5]. Published data from melanoma surveillance cohorts define different thresholds, including: more than 50 nevi or three atypical nevi [53], more than 100 nevi or ten atypical nevi [54], at least one invasive melanoma [6], a melanoma diagnosed before age 40 or two before age 65 [55], or a pathogenic variant in a high-penetrance gene [55].

The deep imaging phenotype aims to define an automated and objective assessment of personalized melanoma risk factors to guide surveillance requirements. The components of the deep imaging phenotype, such as number, size and distribution of nevi, skin tone, photodamage, freckling, and associated genetic information, may be combined into a holistic risk stratification score to customize surveillance. For example, low-risk individuals may benefit from education on performing self-skin examinations, whereas greater risk scores would indicate a need for regular clinician examination, as well as imaging with TBP and sequential digital dermoscopy. As an understanding of the deep imaging phenotype expands, risk stratification may be tailored towards specific diagnoses, such as lentigo maligna melanoma in older photodamaged individuals or amelanotic melanoma in fairly pigmented or genetically predisposed individuals, and includes the risk for keratinocyte cancers that may be simultaneously detected during skin examination [7]. In parallel to risk stratification, the deep imaging phenotype may be implemented in the diagnostic assessment of specific lesions to contextualize the individual's holistic risk, and specific peri-lesional skin topography [7]. Validation and implementation of the deep imaging phenotype will require multidisciplinary teams, robust methodology within clinical trial frameworks, and diverse cohorts. Validation should address practical methods surrounding the implementation of deep image phenotyping including the timing of first risk assessment and frequency thereafter. Optimal timing of first assessment should pre-empt early onset melanoma that may occur in adolescence or early adulthood in genetically predisposed individuals, whilst avoiding excessive enrolment of young, low-risk individuals [56]. Traditional risk factors relating to pigmentation traits, behaviors, and family history may guide the timing of first and ongoing assessments, similar to how these variables influence current recommendations for commencing skin cancer examination [57]. The deep image phenotype risk assessment will require clinical interpretation and follow-up, although guidelines will need to be established as to whether responsibility rests with the referring clinician, operator of the 3D-TBP device, or a centralized service [7]. No cost analysis studies have been published on 3D-TBP outside of high-risk melanoma cohorts given that

the technology remains in a rapidly changing pre-clinical stage [7, 58]. Existing global networks of high [55, 59] and population [60, 61] risk research cohorts present established frameworks that may facilitate prospective trials. Expert consensus-based guidelines will be critical to standardize research frameworks to facilitate future meta-analysis and clinical implementation. Guidelines are currently available to inform methodology for machine learning from TBP [62] and evaluation of image-based AI in dermatology [63].

3.2. Dynamic risk assessment

Risk stratification using the deep imaging phenotype could facilitate dynamic assessment based on the evolution of cutaneous topology factors with age, and updated with clinical information regarding new diagnoses. This provides opportunity to integrate longitudinal data in risk prediction, while recognizing that different risk factors are relevant at different ages. Phenotypes for freckling may be of greater predictive value in early age before fading, whereas photodamage may have greater relevance in older age after many years of ultraviolet exposure [7]. The phenotype for nevi may mature with age. Studies following high- and population-risk individuals over 15 years report an increase in the nevus count and size with greater age, in a distribution favoring the upper body [64, 65]. Therefore, clinical implementation of the deep imaging phenotype will likely require interpretation relevant to the age of the individual. Older individuals are more likely to have established skin phenotypes, whereas, younger individuals with a genetic predisposition may have an evolving phenotype that could be identified prior to the incidence of a first melanoma diagnosis. Clinical information such as family history and genetic profiling may assist in identifying individuals who benefit from early surveillance [66]. After the first phenotyping, the interval to the next repeat assessment would likely be guided by risk status.

3.3. Prevention strategies

Evaluation of the deep imaging phenotype must consider recommendations for individuals determined to be at low risk for melanoma and other cutaneous malignancies. Broad population-based studies will be required to calibrate risk stratification algorithms to a level that constitutes low risk for the specific geographic and demographic characteristics of the region [7]. Education, skin-self examinations, and sun-smart behaviors remain important interventions for individuals even with a low risk for melanoma. Education conducted in a workshop-style format in schools detailing risks and preventative strategies for cutaneous malignancies has demonstrated to impart sun-smart behavioral modifications that persist at least 12 months after completion [67]. Observationally, skin-self examination facilitates the detection of approximately 50% of current melanoma diagnoses, including a disproportionate number of rapid-growing lesions with high mitotic rates and nodular histopathology [68]. Thus, standardized recommendations for skin self-examination and sun-smart behaviors should be established to ensure that all individuals have actionable and evidence-based recommendations based on their specific risk strata.

3.4. Teledermatology

Teledermatology services are an increasingly important modality to improve access to specialist dermatology care. Evidence-based validation of these services supports diagnostic and treatment accuracy whilst maintaining cost-effectiveness [69]. Teledermatology is particularly relevant for melanoma surveillance given that rural and remote populations present with a greater burden of advanced melanoma [70]. The deep imaging phenotype is well-suited for teledermatology models given the increasing adoption of 3D-TBP infrastructure, and that it does not require an in-person clinical examination [7]. Improving accessibility to advanced risk stratification may reduce travel requirements and therefore contribute to addressing health disparities. Cost effectiveness may further be improved based on evidence that both teledermatology [69] and targeted screening of high-risk melanoma patients may reduce costs compared to standard care [58].

4. Challenges and future directions

4.1. Clinician and consumer trust

Successful implementation of a deep imaging phenotype protocol for broad population-based or individual risk stratification will be dependent on consumer and clinician trust. A major barrier to this trust is the 'black box' problem, referring to the lack of transparency regarding how an algorithm arrived at a diagnostic decision [71]. The 'black box' is relevant due to the complexity of image-based algorithms, that utilize multiple layers of computational processes to reach a diagnosis which are not readily interpretable [71]. Interpretability is essential given that algorithm performance is highly reliant on the quality and representativeness of the training data, and that there is a high risk for an algorithm overfitting to specific patterns. For example, a Clever Hans Predictor describes an image feature that is highly correlated to the correct diagnosis, and therefore utilized by an algorithm in lieu of true diagnostic criteria [72]. One Clever Hans Predictor for cutaneous malignancy is photodamage, which is highly correlated to a diagnosis of malignancy, but not a diagnostic feature in itself [73]. Others may include pen markings or lighting conditions that are inadvertently applied to lesions of a specific diagnosis, and therefore overfitted by an algorithm [72]. Minimization of the 'black box' problem for the deep imaging phenotype will be reliant on the experience of the clinician-in-loop, to verify an algorithm output with 3D-TBP, rather than relying on algorithm output alone.

Augmented intelligence describes a framework where AI recommendations are provided as a report to be verified by the clinician [73]. The rationale is that diagnostic accuracy and trust are maximized by clinician decision-making that is supported by AI, rather than a clinician or AI in isolation. This collaborative approach is perceived to be more reliable by patients than examination by dermatologist alone, and even more so than AI alone [74]. However, further research is required to define the optimal framework and workflow for this collaboration. The format of AI recommendations is critical for clinical interpretation and must provide sufficient information. For example, clinician accuracy is improved when provided with multiclass probabilities for a broad range of possible diagnoses, but not improved when provided with simplistic benign vs

malignant or single most likely diagnosis [73]. For experienced clinicians, diagnostic accuracy was only improved with AI recommendations if there was low confidence in the initial diagnosis. Conversely, less experienced clinicians tended to accept AI recommendations regardless of the agreement with their initial diagnosis, and regardless of the confidence in that diagnosis [73]. Clinicians of all experience had reduced accuracy when misled by intentionally incorrect AI recommendations [73, 75]. Clinician experience and interpretable AI output are therefore critical components for future implementation considerations.

4.2. Ethical considerations

The psychological consequences of risk stratification that labels large numbers of individuals as high or low risk for cutaneous malignancy must be considered. Individuals identified as high risk may be at greater risk of psychological distress and maladaptive coping strategies, whereas low risk individuals may disregard sun-smart behaviors [76]. Randomized controlled trials exploring genetic risk stratification for melanoma have shown high-risk individuals reported reduced melanoma-related worry and increased sun-smart behaviors, while low-risk individuals reported no change in sun-smart behaviors, and neither group showed a change in general psychological status [77, 78]. Notably for individuals with a personal history of melanoma, melanoma-related worry does not appear to be modified by stage at diagnosis, reflecting perceptual differences between the patient and clinician [76]. Therefore, a greater understanding is required of the psychosocial impact of risk stratification from a clinician and patient or consumer standpoint.

Legally, clinicians that opt to integrate AI into clinical practice are likely to assume the liability for its role in clinical decisions. Case law suggests that the clinician is accountable for their use of AI recommendations, although, liability may in some cases extend to the device manufacturer and supplier [79]. To navigate the implementation of AI clinical tools, a clinician should gain patient consent and make 'disclosures which a reasonable medical practitioner would make under the same or similar circumstances' according to a consensus review of medical case law for AI [79, 80]. Risk stratification algorithms using AI have remained in research settings to date, and what constitutes 'reasonable disclosures' will likely be led by specialized melanoma units, multidisciplinary guidelines, and transparent input from device manufacturers and consumers. Undoubtedly, AI tools actioned by a clinician-in-loop are likely to provide greater safety nets than patient self-assessment using online risk stratification algorithms [27].

4.3. Data management

Effective and secure data management is essential for the development and implementation of the deep imaging phenotype for melanoma risk stratification. The Digital Image Communication in Medicine (DICOM) is the standard for the storage, linkage with meta-data, and secure sharing of medical images that is near ubiquitously used in image-producing fields such as radiology and cardiology [7]. A dermatology extension was not introduced to DICOM until 2020 given that most images were captured on non-standardized devices and did not require linkage to meta-data [81]. The rationale for the dermatology

DICOM extension was largely driven by AI workflows that benefit from images linked to meta-data, such as mapping to the image location of a patient's body, clinical risk factors for contextualization, and information on the specific diagnosis [81]. Integration with DICOM infrastructure will facilitate interoperability between data, AI analysis, and clinical interpretation, although, it will require detailed regulatory considerations prior to widespread implementation.

Privacy must be of central importance for storage of dermatology images and clinical data. Dermatology images are unique given the difficulty of de-identifying nudity or personal markings (e.g. tattoos, scars) without compromising the clinical utility of the data. Standardized DICOM confidentiality profiles such as those used in radiology to guide which attributes should be removed from images to ensure privacy, could be adapted for dermatology images such as 3D-TBP [81]. Linkage of dermatology images with personal risk factors provides additional identifying data which must be protected. Therefore, implementation of deep imaging phenotyping must be built upon standardized and secured infrastructure, and include detailed participant consent regarding the inclusion of personal data in future research.

5. Conclusions

Risk stratification for melanoma aims to prospectively identify individuals likely to develop a melanoma for targeted screening [7]. However, current methods have limited accuracy in identifying high-risk individuals due to subjective and self-reported measures that are vulnerable to recall bias and poor reproducibility [8]. Inaccurate risk measurements may result in inappropriate screening recommendations, including the over-screening of low-risk individuals, and delayed diagnosis in high-risk individuals [4]. Personalized risk stratification using the deep imaging phenotype aims to address this shortfall through an expanding suite of algorithms that automatically report nevus characteristics (counts, size, distribution), photodamage (severity and distribution), skin tone (innate and facultative), and freckling as objective and holistic risk factors for melanoma [7]. Challenges remain in achieving clinical implementation including calibration of algorithms to specific populations, guidelines for individuals across all risk strata, interpretability of AI output, and ensuring equitable access to technologies [7]. Accounting for the deep imaging phenotype may improve tailored screening recommendations, target resource allocation, and improve outcomes for high-risk individuals.

Additional information

Conflict of interest

HPS is a shareholder of MoleMap NZ Limited and e-derm consult GmbH and undertakes regular teledermatological reporting for both companies. HPS is a Medical Consultant for Canfield Scientific Inc., Blaze Bioscience Inc., MoleMap Australia Pty Limited, and a Medical Advisor for First Derm. No other authors have conflicts to declare.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

Conceptualization: MJ, CR, CP, HPS, SK. Data curation: SK. Formal analysis: SK. Methodology: SK. Supervision: CP. Writing – original draft: CP, SK. Writing – review and editing: MJ, HPS, CP, SK, CR.

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Data availability

All of the data that support the findings of this study are available in the main text.

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