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Article

Comparison of MOLES and MelAI_{noma} for Differentiating Small Choroidal Melanomas from Nevi

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Simple Summary

Small eye melanomas can be difficult to distinguish from harmless pigmented spots in the back of the eye, called choroidal nevi. Because the risk of cancer spread increases as melanomas grow, early and accurate identification is important, but unnecessary referrals and treatment should also be avoided. Tools that support non-expert clinicians in deciding which lesions need specialist evaluation are therefore increasingly important. In this study, we compared two such tools: the MOLES scoring system, which is manually applied using several eye imaging methods, and MelAI_{noma}, an artificial intelligence system that analyzes a single color photograph of the eye. We examined how closely the two methods agree and how well each is associated with expert diagnosis of melanoma. Both tools were useful, but they captured partly different information. MelAI_{noma} showed a slightly stronger association with diagnosis despite using less imaging data, suggesting a potential role as a complementary aid for lesion triage.

Abstract

Background: Early identification of small choroidal melanomas is important, as metastatic risk increases with tumor size. However, distinguishing small melanomas from benign choroidal nevi is challenging and may lead to unnecessary referrals and overtreatment. Both the MOLES scoring system and the deep learning algorithm MelAI_{noma} have been developed to support assessment of pigmented choroidal lesions in non-expert settings. This study aims to compare the association between MOLES and MelAI_{noma} scores and to assess their relative association with expert melanoma versus nevus diagnosis. **Methods:** In this retrospective cohort study, 86 patients with small pigmented choroidal lesions (29 melanomas and 57 nevi) diagnosed at a national ocular oncology referral center were included. MOLES scores were assigned by ocular oncologists based on multimodal examination, whereas MelAI_{noma} scores were generated solely from color fundus photographs. Associations between scores were assessed using linear regression and the Jonckheere–Terpstra test. Univariable and multivariable binary logistic regression was used to evaluate associations with melanoma diagnosis. **Results:** MelAI_{noma} scores increased monotonically with higher MOLES categories ($P=0.0001$). Linear regression showed a statistically significant association between MOLES and MelAI_{noma} scores, but with substantial dispersion ($R^2=0.16$). In univariable logistic regression, both MOLES and MelAI_{noma} scores were associated with increased odds of melanoma diagnosis. MelAI_{noma} showed a stronger association with diagnosis than MOLES ($R^2=0.38$ vs. 0.27). In multivariable analysis including both scores, each remained independently associated with melanoma diagnosis. **Conclusions:** Both MOLES and MelAI_{noma} are effective for differentiating small choroidal melanomas from nevi. Although the scores are statistically associated, they capture partly distinct information. MelAI_{noma} demonstrates slightly stronger association with melanoma diagnosis and provides fully reproducible output, supporting its role as a complementary aid in lesion triage.

Keywords: choroidal melanoma; uveal melanoma; choroidal nevus; MelAInoma; MOLES; artificial intelligence; deep learning; fundus photography; ocular oncology

1. Introduction

The risk of metastasis in uveal melanoma is strongly correlated with tumor size.[1,2] Accurate identification of melanomas when they are as small as possible is therefore likely one of the most effective ways to improve survival in this aggressive disease. However, small choroidal melanomas may be difficult to distinguish from benign pigmented choroidal lesions, which are common in the general population and affect more than 5% of individuals of Caucasian descent.[3,4] Efforts to detect and treat choroidal melanomas at an early stage may therefore result in overdiagnosis and treatment of harmless lesions with potentially severe consequences for visual function.

In Sweden, opticians frequently use optical coherence tomography (OCT) and fundus photography in routine practice.[5] Together with widespread screening for diabetic retinopathy and frequent examinations or treatment for age-related macular degeneration (AMD) or cataract, this has led to detection of an increasing number of incidental pigmented choroidal lesions. As a consequence, a growing number of patients are referred to ocular oncologists, including many false-positive cases. This may pose a challenge, as ocular oncology is a highly specialized field with limited resources, and excessive referrals may delay assessment of patients who truly require intervention.

To support triage of pigmented choroidal lesions in non-expert settings, we have developed a deep learning algorithm, MelAInoma, which estimates the probability that a lesion represents a melanoma based on fundus photographs.[6] In prior evaluations, MelAInoma achieved higher diagnostic accuracy than ocular oncologists, consultant ophthalmologists, and resident ophthalmologists when classifying fundus images, using multimodal expert assessment as reference.[6] When applied by opticians and optometrists, MelAInoma quadrupled the odds of correctly referring a melanoma, reduced false-positive referrals tenfold, and provided net clinical benefit compared with unaided triage.[5]

In contrast, the MOLES system is a well-established, manually applied scoring system designed to support non-expert monitoring of pigmented choroidal lesions and referral decisions.[7,8] MOLES is widely used by opticians and ophthalmologists. By assessing and grading five visual risk factors for growth, lesions are classified as common nevus, low-risk nevus, high-risk nevus, or probable melanoma.[8]

In the present study, we use MOLES scores assigned by ocular oncologists and compare these with MelAInoma scores generated from fundus photographs. We then examine how each of these scores correlates with the true diagnosis, as established by subspecialized ocular oncologists, and assess their relative association with melanoma versus nevus classification.

2. Materials and Methods

2.1. Aim of the Study

The aim of this study is to examine whether MOLES and MelAInoma scores correlate, and to assess which of the two is more strongly associated with a diagnosis of choroidal melanoma versus choroidal nevus.

2.2. Patients and Lesions

This study included a cohort of 86 patients with one pigmented choroidal lesion each, diagnosed as either small choroidal melanoma or choroidal nevus at St. Erik Eye Hospital, Stockholm, Sweden. This study was approved by the Swedish Ethical Review Authority (reference 2025-05054-01) and adhered to the tenets of the declaration of Helsinki.

Inclusion criteria were as follows:

1. Age >18 years at the time of examination.
2. Fundus photograph obtained after January 1, 2010, corresponding to a period when medical records were fully digitalized, facilitating reliable assessment of follow-up.
3. Diagnosis of either choroidal melanoma (International Classification of Diseases, 10th Revision [ICD-10] code C69.3) or choroidal nevus (ICD-10 code D31.3).
4. Diagnosis established by a subspecialized ocular oncologist.
5. For lesions classified as nevi at the time of photography, a minimum of 5 years of follow-up without reclassification as melanoma was required. Lesions that were diagnosed as melanoma at a later time point (e.g., due to documented growth) were classified as melanomas in the present study. This criterion was applied to facilitate detection of early signs of malignancy at a stage when small melanomas are difficult to distinguish from nevi.

Exclusion criteria were:

1. Fundus photographs of insufficient quality, where factors such as poor focus, motion artifacts, over- or underexposure, or reflections prevented reliable assessment of lesion extent or the presence of features such as orange pigment or drusen. Minor image imperfections that did not impede assessment (e.g., focal blur or limited overexposure) were not sufficient for exclusion.
2. Photographs in which less than half of the lesion was visible, acknowledging the limitation in accurately estimating the extent of the non-visible portion.
3. Lesions obscured by retinal detachment, vitreous hemorrhage, or similar conditions.

The included lesions were imaged using either a standard-field fundus camera (45° field of view; Canon Medical Systems Europe B.V.; $n=55$) or an ultra-widefield camera (pseudocolor images covering 200°; Optos Inc.; $n=31$). This cohort has been described in detail previously, including the multimodal diagnostic workup used by ocular oncologists, as it was employed as a test cohort during the development and validation of the MelAI_{noma} algorithm.[6] The cohort was not used for development or training of the MelAI_{noma} deep learning model.

2.3. MOLES

MOLES is a clinical scoring system based on five features: Mushroom shape, Orange pigment, Large size, Enlarging tumor, and Subretinal fluid. Each feature is assigned a score of 0, 1, or 2, reflecting absence, borderline presence, or definite presence.[7,8] Mushroom shape is highly suggestive of choroidal melanoma and is included to ensure referral even in absence of other suspicious features. Orange pigment has been identified as an important risk factor for growth of melanocytic lesions, despite occurring in other choroidal conditions.[9,10] Large size is included because most choroidal nevi are small; in population-based studies, the mean largest basal diameter is approximately 1.25 mm, only a minority exceed 5.5 mm, and increased thickness is associated with a higher risk of future growth.[11] Although choroidal nevi may enlarge slowly over an extended period, more rapid growth is suggestive of malignant transformation.[12] Subretinal fluid is also included, as it has consistently been associated with lesion growth. Based on the total score, lesions are categorized as common nevus (score 0), low-risk nevus (score 1), high-risk nevus (score 2), or probable melanoma (score >2).[8] In this study, all MOLES scores were assigned by ocular oncologists at St. Erik Eye Hospital, with access to multimodal imaging for each lesion to assess the presence of risk factors, such as OCT for detection of subretinal fluid and autofluorescence for identification of orange pigment. In contrast, MelAI_{noma} scores were based solely on analysis of color fundus photographs of the lesion.

2.4. Statistical Analyses

Associations between MOLES score and MelAI_{noma} score were evaluated using linear regression. As MOLES score is an ordinal variable and MelAI_{noma} score is continuous, an ordered trend was additionally assessed using the Jonckheere–Terpstra test, which does not assume normality. To evaluate the association between each score and diagnostic outcome, binary logistic regression was performed with true diagnosis (melanoma vs. nevus) as the dependent variable. Odds

ratios (ORs) with 95% confidence intervals (CI) were reported. MelAInoma score and MOLES score were also entered simultaneously as predictors in a multivariable logistic regression model. No interaction terms or variable transformations were included. Model fit was assessed using the Akaike Information Criterion corrected for small sample size (AIC) and by evaluation of calibration with the Hosmer–Lemeshow test. MelAInoma scores were generated by loading fundus photographs into the MelAInoma software (version 0.1; Eyedentity AB, Stockholm, Sweden), which outputs a probability between 0 and 1 that the lesion represents a melanoma. All statistical tests were two-sided, and a significance level of $P<0.05$ was used. Data management and statistical analyses were performed using R version 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 10.6.1 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Descriptive Statistics

The study included 86 patients with 86 pigmented choroidal lesions, of whom 48 (56%) were female. Of the 86 lesions, 57 (66%) were diagnosed as nevi and 29 (34%) as melanomas. Among melanomas, the mean tumor thickness was 2.8 mm and the mean largest basal diameter (LBD) was 6.6 mm. Further cohort characteristics are summarized in **Table 1**.

Table 1. Characteristics of included patients and lesions.

<i>n</i> images	86
<i>n</i> unique patients	86
Sex, <i>n</i> (%)	
Male	38 (44)
Female	48 (56)
Age, mean years (SD)	58 (14)
Fundus photography type, <i>n</i> (%)	
Wide field	31 (36)
Standard field	55 (64)
Nevi, <i>n</i> (%)	57 (66)
Melanomas, <i>n</i> (%)	29 (34)
Nevus LBD, mean mm (SD)	4.4 (1.6)
Nevus thickness, mean mm (SD)	1.6 (0.4)
Melanoma LBD, mean mm (SD)	6.6 (2.1)
Melanoma thickness, mean mm (SD)	2.8 (1.5)
Mean MOLES score (SD)	
Overall	1.6 (2.2)
For nevi	0.7 (1.2)
For melanomas	3.9 (2.4)

LBD, largest basal diameter. SD, standard deviation. MOLES assigns a score of 0, 1, or 2 for Mushroom shape, Orange pigment, Large size, Enlarging tumor, and Subretinal fluid, based on their absence, borderline presence, or presence. Lesions are classified as common nevi, low-risk nevi, high-risk nevi, or probable melanoma, based on their total score being 0, 1, 2, or more than 2, respectively, as described by Roelofs *et al.* 2020.

3.2. Distribution of MelAInoma Scores Across MOLES Scores

MelAInoma scores increased monotonically with increasing MOLES categories. The distribution of lesions by MOLES score was as follows: MOLES 0 ($n=46$), MOLES 1 ($n=8$), MOLES 2 ($n=13$), MOLES 3 ($n=11$), and MOLES ≥ 4 ($n=8$). Using the Jonckheere–Terpstra test to evaluate an ordered trend, there was strong evidence for increasing MelAInoma scores with higher MOLES categories (JT=1620, $P=0.0001$, one-sided test for increasing trend). This association persisted despite substantial ties in

MelAInoma score values and unequal group sizes, indicating a consistent monotonic relationship between MOLES score and AI-based risk estimation (**Figure 1**). In addition, a rank-based one-way ANOVA (Kruskal–Wallis test) showed differences in MelAInoma score distributions across MOLES categories ($P=0.0008$)

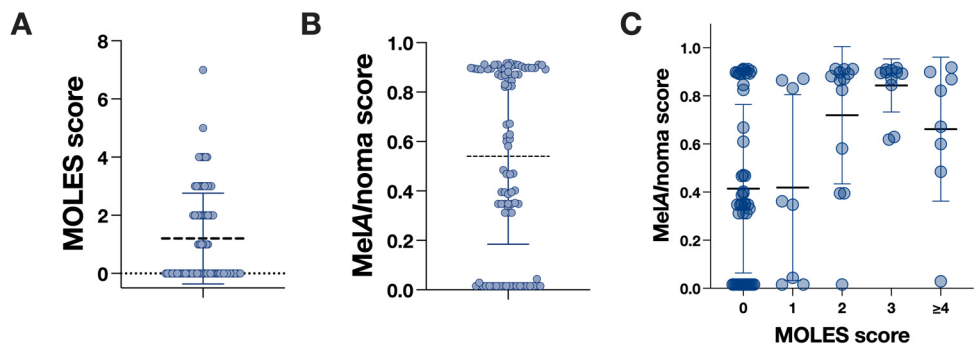


Figure 1. Distribution of MOLES and MelAInoma scores. Each point represents one lesion. (A) Distribution of MOLES scores across the included lesions, shown with horizontal jitter to reduce overlap. The horizontal line indicates the mean, and whiskers indicate the standard deviation (SD). (B) Distribution of MelAInoma scores across the included lesions. (C) Distribution of MelAInoma scores stratified by MOLES score (0, 1, 2, 3, and ≥ 4).

3.3. Linear Regression

In linear regression analysis, increasing MOLES score was associated with higher MelAInoma score (slope 0.09 per MOLES unit, 95% CI 0.05 to 0.14, $P<0.0001$). However, the association showed considerable dispersion, with MOLES score explaining only 16% of the variability in MelAInoma score ($R^2=0.16$, **Figure 2**).

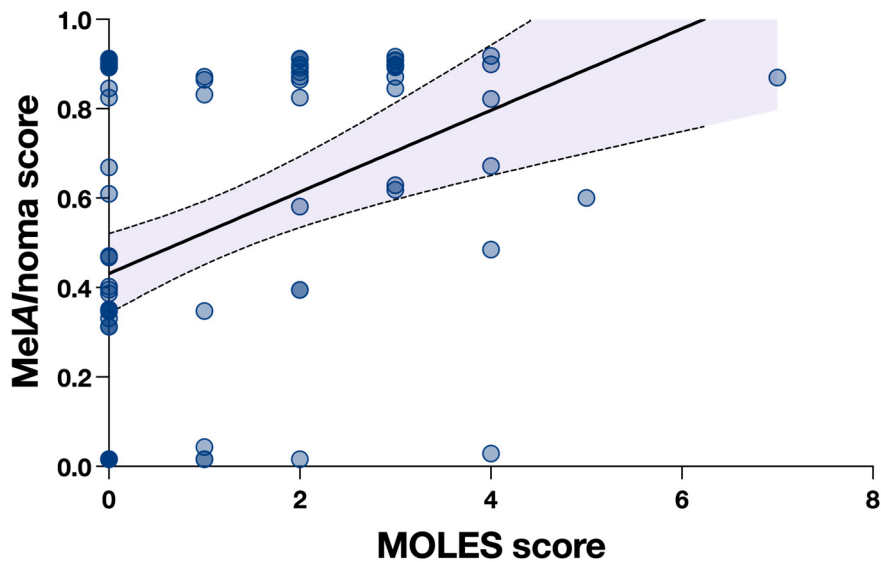


Figure 2. Association between MOLES score and MelAInoma score. Scatter plot showing MelAInoma score as a function of MOLES score. The solid line represents the fitted linear regression (slope 0.09 per MOLES unit; $P<0.0001$), and the shaded area indicates the 95% confidence interval (CI).

3.4. Binary Logistic Regression for MOLES

In binary logistic regression with MOLES score as the sole predictor, higher MOLES score was associated with increased odds of melanoma diagnosis (**Figure 3A**). Each one-unit increase in MOLES score was associated with a more than twofold increase in the odds of melanoma (OR 2.29, 95% CI 1.59 to 3.50, $P < 0.0001$, **Table 2**). Model fit was acceptable, with a Tjur’s R^2 of 0.27.

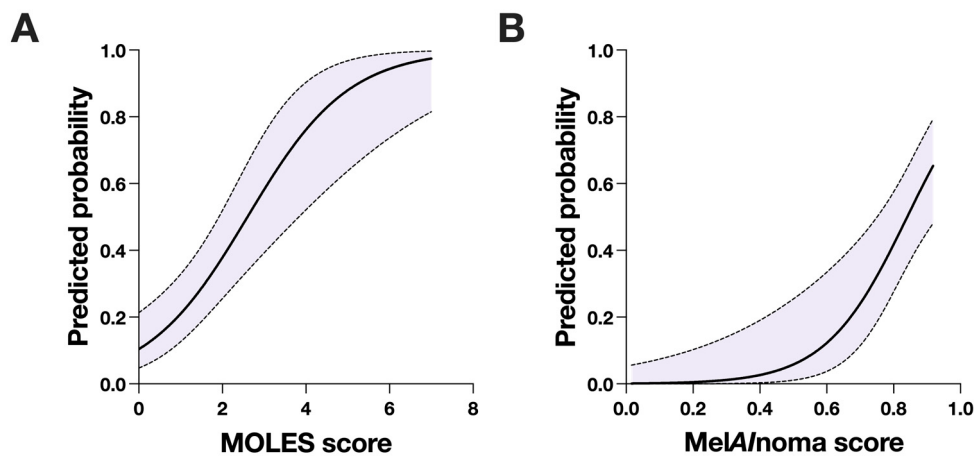


Figure 3. Binary logistic regression models. (A) Predicted probability of melanoma as a function of MOLES score from a binary logistic regression model. (B) Predicted probability of melanoma as a function of MelAInoma score from a binary logistic regression model. In both panels, the solid line represents the fitted model, and the shaded area indicates the 95% confidence interval (CI).

Table 2. Univariable binary logistic regression for MOLES score and melanoma diagnosis.

Predictor	Scale	OR	95% CI	P
MOLES score	Per 1-unit increase	2.29	1.59 to 3.50	<0.0001

Binary logistic regression with true diagnosis as outcome. CI, confidence interval. OR, odds ratio.

3.5. Binary Logistic Regression for MelAInoma

In binary logistic regression using MelAInoma score as the sole predictor, higher MelAInoma score was associated with increased odds of melanoma diagnosis (**Figure 3B**). When scaled per 0.1-unit increase, the odds of melanoma increased by a factor of 2.27 (OR 2.27 per 0.1 increase, 95% CI 1.57 to 4.23, $P < 0.0001$, **Table 3**). Compared to the MOLES model, this model explained a larger proportion of outcome variability (Tjur’s $R^2 = 0.38$).

Table 3. Univariable binary logistic regression for MelAInoma score and melanoma diagnosis.

Predictor	Scale	OR	95% CI	P
MelAInoma score	Per 0.1 increase	2.27	1.57 to 4.23	<0.0001

Binary logistic regression with true diagnosis as outcome. CI, confidence interval. OR, odds ratio.

3.6. Multivariable Binary Logistic Regression

In multivariable binary logistic regression including both MOLES score and MelAInoma score, both predictors remained associated with melanoma diagnosis. After adjustment for MOLES score, each 0.1-unit increase in MelAInoma score was associated with a 2.82-fold increase in the odds of melanoma (OR 2.82, 95% CI 1.62 to 6.85, $P < 0.0001$, **Table 4**). MOLES score also remained associated with melanoma diagnosis after adjustment for MelAInoma score (OR 2.24 per one-unit increase, 95% CI 1.40 to 4.02, $P = 0.002$). The combined model showed substantially improved the fit compared with

the intercept-only model (AIC 55.3 vs. 103.2), and there was no evidence of poor calibration based on the Hosmer–Lemeshow test ($P=0.86$).

Table 4. Multivariable binary logistic regression for melanoma diagnosis.

Predictor	Scale	OR	95% CI	P
MelAInoma score	Per 0.1 increase	2.82	1.62 to 6.85	<0.0001
MOLES score	Per 1-unit increase	2.24	1.40 to 4.02	0.002

Binary logistic regression including both MOLES score and MelAInoma score as predictors. No interaction terms or variable transformations were included. CI, confidence interval. OR, odds ratio.

3.7. Sensitivity Analysis by Imaging Modality

To determine if the AI algorithm’s performance remained stable across different clinical presentations and imaging hardware, a subgroup analysis was performed. Lesions were categorized based on whether they were captured with standard-field or ultra-widefield systems. It should be noted that while MelAInoma scores were derived solely from these color photographs, MOLES scores were established by ocular oncologists with access to multimodal imaging (e.g., OCT and autofluorescence). In the standard-field subgroup, MelAInoma achieved an AUC of 0.87 (95% CI 0.78–0.96) compared to 0.80 (95% CI 0.67–0.93) for MOLES with no statistically detectable difference between the methods ($P=0.42$, DeLong test). Similarly, in the ultra-widefield subgroup, MelAInoma achieved an AUC of 0.87 (95% CI 0.72–1.00) compared to 0.79 (95% CI 0.61–0.97) for MOLES ($P=0.48$). These findings indicate that MelAInoma maintains a high and stable diagnostic accuracy across different clinical subgroups, even when compared to an expert scoring system supported by multimodal data.

4. Discussion

In this study, we demonstrate that both the MOLES system and the MelAInoma algorithm were associated with melanoma diagnosis in a cohort of small pigmented choroidal lesions. The two systems demonstrated a statistically significant association, and higher values of either score were linked to higher odds of melanoma. This is clinically relevant, as both approaches are intended for use by non-expert opticians, optometrists, and ophthalmologists in settings where early triage of suspicious lesions is increasingly important.

Despite this overall concordance, there were notable differences between the two systems. Although the association between MOLES and MelAInoma scores was statistically significant, linear regression displayed substantial dispersion, with MOLES explaining only a limited proportion of the variability in MelAInoma score. This suggests that, while related, the two systems capture overlapping but not identical information. In univariable binary logistic regression, MelAInoma showed slightly stronger associations with melanoma diagnosis than MOLES. This difference may partly reflect the distributional properties of the two scores: MOLES values were heavily clustered at low scores, whereas MelAInoma scores were more continuously distributed across lesions, allowing for greater separation in estimated odds across the range of values.

In multivariable logistic regression, both MOLES and MelAInoma scores remained associated with melanoma diagnosis after adjustment for one another, indicating that each score contributed information beyond the other. Although the statistical evidence was slightly stronger for MelAInoma, the results do not suggest that one system renders the other obsolete. Rather, they indicate that the two approaches reflect partly distinct aspects of lesion assessment.

A notable finding of this study is the information efficiency demonstrated by the MelAInoma algorithm. While the expert graders assigned MOLES scores with the benefit of multimodal imaging—including OCT for subretinal fluid and autofluorescence for orange pigment—the AI algorithm achieved a higher point estimate for AUC using only a single color fundus photograph. This suggests that the deep learning model captures diagnostic features from standard photography

that are at least as predictive of treatment-requirement as the high-resolution features identified by experts using specialized equipment. In primary care or optometric settings where OCT and AF are often unavailable, this ability to provide high-level risk stratification from a simple photo represents a significant clinical advantage.

An additional practical distinction between the systems is that MelAI_{noma} provides fully reproducible output, yielding the same score each time a given image is analyzed, independent of the user. In contrast, MOLES scoring is subject to human interpretation. In the present study, all MOLES scores were assigned by experienced ocular oncologists, effectively establishing a performance ceiling for the manual scoring system. Because previous research has shown that MOLES performance can vary significantly based on observer expertise, it is probable that the diagnostic gap between the two systems would be even more pronounced in the primary care settings for which they are intended, where the AI's consistency would remain stable while manual scoring accuracy might decline.[5,6]

Another conceptual difference is that MelAI_{noma} does not explicitly base its classification on predefined clinical risk factors for growth. Although such factors are well established and clinically useful, they do not necessarily reflect underlying tumor biology, including genetic and cytogenetic alterations known to be associated with prognosis.[13,14] Whether image-based AI systems such as MelAI_{noma} capture information related to these biological features remains an open question. Future work should therefore evaluate how MelAI_{noma} scores relate to genetic and cytogenetic markers, such as monosomy 3 and *BAP1* mutation status, and aim to identify new image-derived risk features that more accurately reflect tumor biology.[15,16]

4.1. Strengths and Limitations

This study has several limitations. First, it was based on a relatively small cohort from a single national referral center. Although images were acquired using both standard-field and ultra-widefield cameras, patients from Sweden may not be representative of other populations,[17,18] limiting generalizability. Second, genetic and cytogenetic data were not available, precluding analysis of associations with established molecular prognostic factors. Third, both diagnoses and MOLES scores were established by subspecialized ocular oncologists. Results may therefore differ if diagnoses and scoring were performed by non-experts, a scenario that would likely disadvantage MOLES more than MelAI_{noma}. Since the same expert group assigned MOLES scores and established diagnoses, some degree of bias toward stronger associations between MOLES and diagnosis cannot be excluded. Specifically, the high level of clinical expertise in this study may have inadvertently compensated for the inherent subjectivity of the manual MOLES criteria, a factor that might not be present in a real-world triage environment. Fourth, there was an asymmetry in the data available to each system; while MOLES scoring was supported by multimodal imaging, MelAI_{noma} was restricted to color fundus photography. Consequently, this study could not evaluate whether the addition of OCT or autofluorescence data would further enhance the algorithm's performance. Furthermore, while the current results demonstrate the AI's efficacy as a standalone triage tool, its integration with other clinical data remains a subject for future investigation.

The study also has several strengths. The cohort was independent of the datasets used to develop and train the MelAI_{noma} algorithm. Diagnoses were established using multimodal expert assessment, including ultrasonography, OCT, biomicroscopy, and fundus imaging. In addition, classification of lesions as nevi required at least five years of follow-up without reclassification as melanoma, increasing confidence in the correctness of the ground truth diagnoses.

5. Conclusions

Both MOLES and MelAI_{noma} are useful tools for differentiating small choroidal melanomas from nevi. The two systems are statistically associated and both are linked to the odds of melanoma diagnosis. MelAI_{noma} offers practical advantages related to reproducibility and demonstrated slightly stronger associations with melanoma diagnosis in this cohort. These findings support the

potential role of MelAInoma as a complementary aid in the assessment and triage of pigmented choroidal lesions.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Swedish Ethical Review Authority (reference 2025-05054-01, date of approval September 3, 2025).

Informed Consent Statement: Patient consent was waived as this was a retrospective study that does not affect the treatment or follow-up of the patients. Further, all patient data and images had been previously collected and no new clinical data collection was performed, and no biological tissues were analyzed.

Data Availability Statement: Due to the sensitive nature of the clinical data, including images utilized in this study, the authors are unable to share these materials in compliance with Swedish law. The confidentiality and privacy regulations governing patient information strictly prohibit the distribution of such data.

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Conflicts of Interest: Mats Holmström and Gustav Stålhammar are founders of Eyedentity AB and hold equity in the company, which develops the MelAInoma software evaluated in this study.

Abbreviations

The following abbreviations are used in this manuscript:

AI	Artificial intelligence
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
AMD	Age-related macular degeneration
AUC	Area under the curve
CI	Confidence interval
MOLES	Mushroom shape, Orange pigment, Large size, Enlarging tumor, and Subretinal fluid
OCT	Optical Coherence Tomography
OR	Odds ratio
LBD	Largest basal tumor diameter
SD	Standard deviation

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