ORIGINAL ARTICLE

Diagnostic Yield of Skin Biopsies Submitted to Rule Out Melanoma

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ABSTRACT

Background: The phrase “rule out melanoma” (ROM) frequently appears on pathology requisitions, potentially influencing diagnostic thresholds and clinical management. Despite widespread use, the diagnostic yield and implications of ROM terminology remain under-investigated.
Objective: To assess the diagnostic yield and histopathologic outcomes of skin biopsies labeled ROM, and to evaluate differences in melanoma detection accuracy across healthcare provider types.
Methods: In this retrospective observational study, we analyzed 12,852 skin biopsy specimens submitted to Cockerell Dermatopathology during 2024 with requisitions explicitly containing ROM language. Diagnostic yields, melanoma subtypes, and alternative diagnoses were documented. Provider-specific diagnostic accuracy was compared using Chi-squared and Fisher’s exact tests.
Results: Of 12,852 biopsies labeled to ROM, 1,724 (13.41%) were histologically confirmed as melanoma. Melanoma in situ accounted for the majority (74.4%) of confirmed melanoma cases, followed by malignant melanoma (18.5%) and metastatic melanoma (7.1%). Among non-melanoma diagnoses, dysplastic nevi (24.8%) and seborrheic keratoses (18.9%) were the most common. Diagnostic accuracy varied significantly by provider specialty ($p < 0.001$), with medical doctors exhibiting the highest melanoma detection rate (15.77%), followed by nurse practitioners (11.34%), Doctor of Osteopathic Medicine (10.79%), and physician assistants (8.67%).
Conclusion: The use of ROM terminology on pathology requisitions on pathology requisitions has a low positive predictive value for melanoma diagnosis. Significant variability in melanoma detection rates across provider types suggests the potential for improved clinical decision-making and requisition practices to minimize overdiagnosis and diagnostic burden.

INTRODUCTION

Cutaneous melanoma is a potentially lethal malignancy [1] that accounts for the vast majority of skin cancer related deaths, despite comprising a small fraction of total skin cancer cases.[2] Early detection remains the cornerstone of effective melanoma control [3], with prognosis strongly correlated to Breslow depth and mitotic activity at the time of diagnosis.[4] In response, public health

campaigns and the widespread integration of skin cancer screening into routine clinical practice have driven efforts to identify melanoma at earlier, more treatable stages.[5] While these efforts have likely contributed to earlier diagnoses, they have also been accompanied by a marked increase in skin biopsy volume, particularly of lesions with low pretest probability of malignancy.[6] This trend has been paralleled by rising rates of thin and in situ melanoma diagnoses, without a proportionate decline in overall melanoma mortality [7] raising concerns about overdiagnosis and the unintended consequences of diagnostic escalation. Amid this increase in biopsies for low-probability lesions, the phrase “rule out melanoma” (ROM) has become a common entry on pathology requisition forms, reflecting a heightened clinical suspicion even in cases with low likelihood of malignancy.

ROM language, though often intended to convey diagnostic caution, may exert interpretive pressure on dermatopathologists, especially when histologic features are ambiguous. This may inadvertently lower diagnostic thresholds,[8] increase utilization of ancillary tests,[9] prolong turnaround times, and inflate diagnostic costs.[10] It may also contribute to overtreatment and patient anxiety.[11]

Despite its widespread use in clinical practice, the positive predictive value and downstream impact of ROM pathology requests have not been well characterized. In this study, we evaluated the proportion of skin biopsies labeled ROM that resulted in a histopathologic diagnosis of melanoma. We also examined how diagnostic outcomes varied by clinician specialty and characterized the most common alternative histopathologic diagnoses among cases that did not result in melanoma. By evaluating the diagnostic performance associated with ROM requests, our study seeks to provide empirical data that may guide more evidence-based use of melanoma-related language in pathology requisitions.

METHODS

Study Design

Approximately fourth months into the treatment course, at a cumulative dose of 103 mg/kg, the patient developed two alopecic patches on the scalp (**Figure 1A and B**), consistent with alopecia areata. The lesions were treated with intralesional triamcinolone acetonide (3 mg/ml) and isotretinoin was continued. Because the alopecia areata continued to progress despite treatment, a decision was made by the patient and treating physician to discontinue the course of isotretinoin early (at a total cumulative dose of 118 mg/kg) in the event that isotretinoin was contributing to his worsening alopecia. Affected lesions were again injected with intralesional triamcinolone acetonide (this time at a dose of 5 mg/ml), and the patient was started on topical augmented betamethasone 0.05% lotion and pulse-dose oral dexamethasone 4 mg daily on Saturday and Sunday.

Patient Selection

Eligible cases included skin biopsy specimens submitted to Cockerell Dermatopathology, in which the original pathology requisition form contained the phrase “rule out melanoma” or semantically equivalent language such as “concern for melanoma” listed in the clinical differential diagnosis. Cases were excluded if the requisition lacked melanoma-specific phrasing, if clinical documentation or histopathology reports were incomplete, or if multiple biopsies were submitted as it

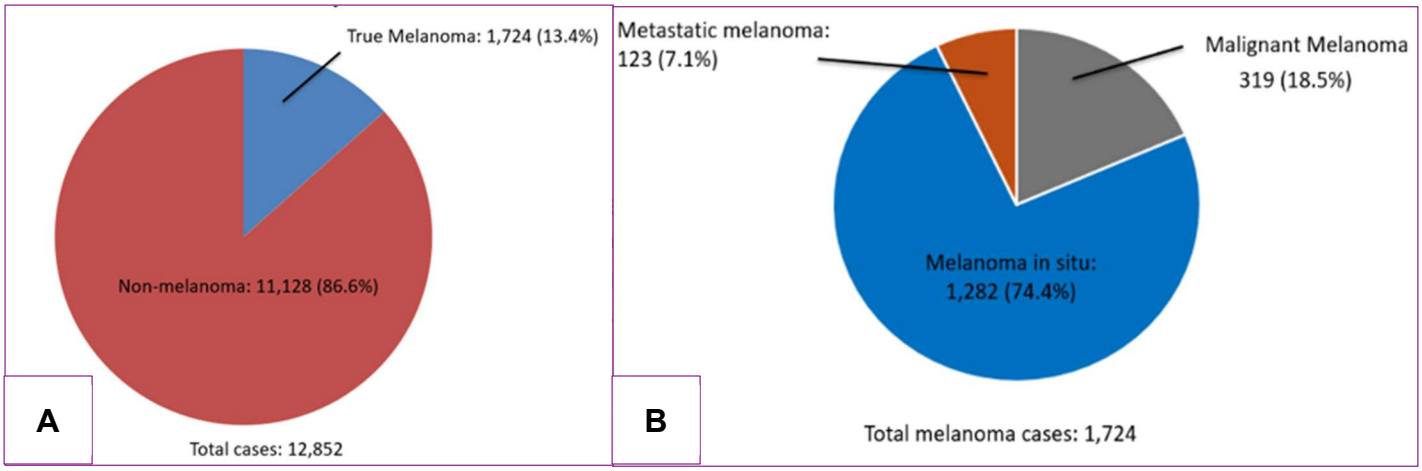

Figure 1. (A) Diagnostic yield of rule-out melanoma biopsies showing the proportion of true melanoma (n = 1,724; 13.4%) and non-melanoma cases (n = 11,128; 86.6%) out of 12,852 total cases and (B) Distribution of melanoma subtypes among biopsy-confirmed melanoma cases, showing melanoma in situ (n = 1,282; 74.4%), malignant melanoma (n = 319; 18.5%), and metastatic melanoma (n = 123; 7.1%)

assistant or nurse practitioner, or other), and the specific melanoma subtype(s) listed on the requisition form, if specified (e.g., melanoma, melanoma in situ, metastatic melanoma). The final histopathologic diagnosis made by the interpreting dermatopathologist was also recorded for each case. All specimens included were reviewed by board-certified dermatopathologists.

Statistical Analysis

Descriptive statistics were used to summarize frequencies of melanoma and non-melanoma histopathologic diagnoses, including subtype distributions. Diagnostic accuracy was defined as the proportion of ROM-labeled biopsies that received a final diagnosis of melanoma.

Comparisons of melanoma detection rates across provider were performed using Chi-square tests for independence. To assess the magnitude of association, effect size was calculated using Cramer's V. A Cramer's V value of 0.1 was considered small, 0.3

Study Population and Diagnostic Yield

During the study period from January 1, 2024, to December 31, 2024, a total of 12,852 skin biopsy specimens were submitted to Cockerell Dermatopathology with pathology requisitions. The average age of patients at biopsy was 62 years of age.
Of the 12,852 rule-out melanoma cases, 1,724 (13.41%) received a final histopathologic diagnosis of melanoma, while 11,128 (86.59%) were diagnosed as non-melanoma lesions (**Figure 1A**).

Melanoma Subtype Distribution

Among the 1,724 confirmed melanoma cases (**Figure 1B**), the majority were melanoma in situ variants. Melanoma in situ diagnoses (including "Residual Melanoma in-situ," "Melanoma in situ," and "Evolving melanoma in situ") accounted for 1,282 cases (74.4% of all melanoma diagnoses). Metastatic melanoma accounted for 123 cases (7.1% of melanoma diagnoses).

Non-Melanoma Diagnostic Patterns

Analysis of the 11,128 cases that did not result in melanoma diagnoses revealed the following diagnostic findings (**Figure 2**). Dysplastic nevus was identified in 2,756 cases (24.8% of non-melanoma diagnoses). Seborrheic keratosis occurred in 2,105 cases (18.9%). Scar tissue was identified in 1,274 cases (11.4%). Basal cell carcinoma was diagnosed in 803 cases (7.2%).

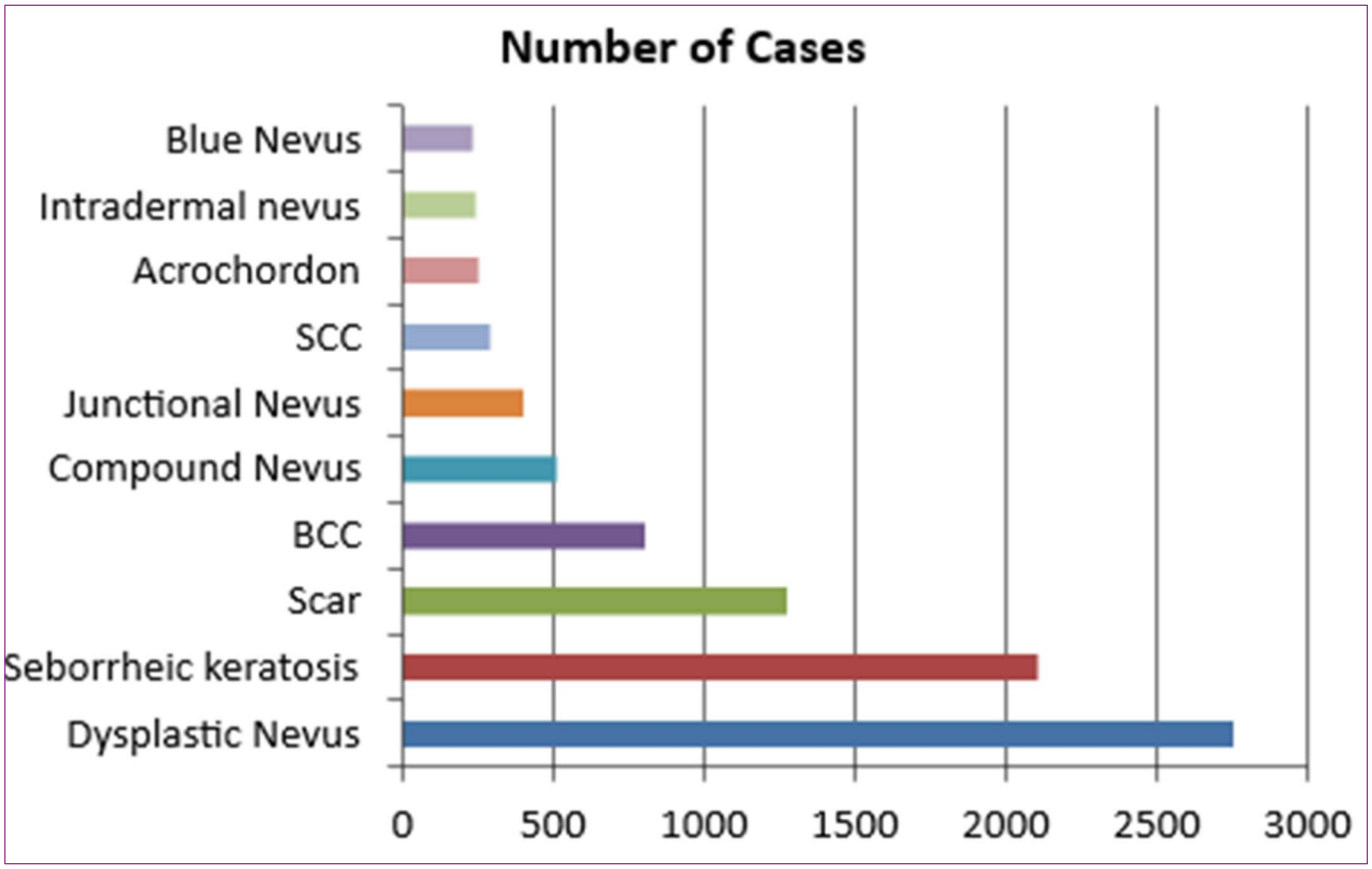

Figure 2. Top ten most common non-melanoma diagnoses from rule-out melanoma biopsies

Additional non-melanoma diagnoses included compound nevus (509 cases, 4.6%), junctional nevus (403 cases, 3.6%), squamous cell carcinoma (292 cases, 2.6%), acrochordon (252 cases, 2.3%), intradermal nevus (242 cases, 2.2%), and blue nevus (231 cases, 2.1%).

Diagnostic Accuracy by Healthcare Provider Type

Diagnostic accuracy varied across healthcare provider types submitting ROM requests (**Figure 3**). Medical doctors (MDs) had 1,293 confirmed melanoma diagnoses out of 8,200 total ROM submissions (15.77%). Nurse practitioners (NPs) had 61 confirmed melanoma diagnoses among 538 total ROM submissions (11.34%). Doctors of osteopathic medicine (DOs) had 64 melanoma cases among 593 total submissions (10.79%). Physician assistants (PAs) had 305 confirmed melanoma diagnoses out of 3,518 total ROM requests (8.67%).

MDs contributed 63.8% of all ROM submissions, PAs contributed 27.4%, DOs contributed 4.6%, and NPs contributed 4.2%.

In terms of provider demographics, our sample consisted of 246 MDs (60.9%), 112 PAs (27.7%), 27 NPs (6.7%), and 19 DOs (4.7%) out of 404 total providers.

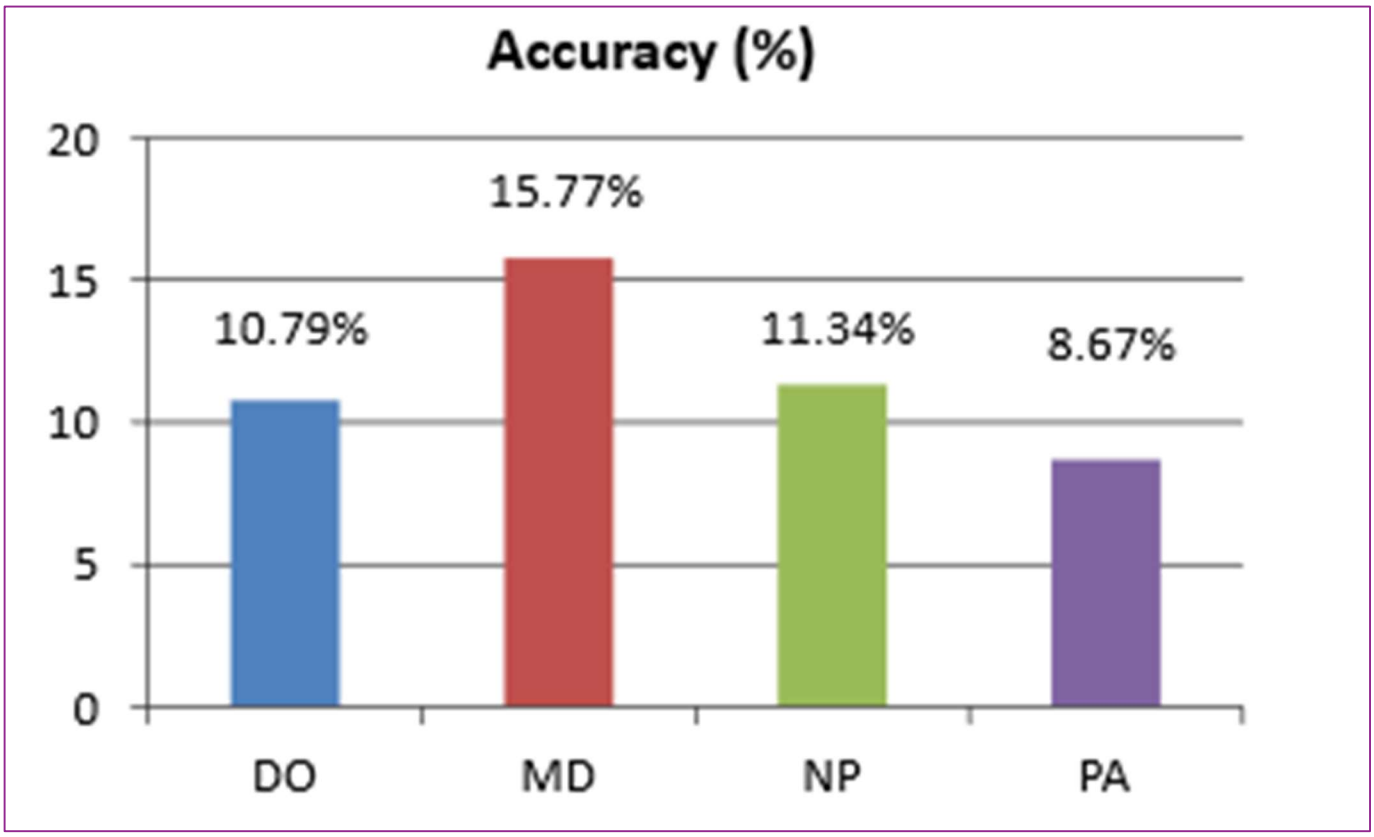

Figure 3. Melanoma diagnostic accuracy stratified by provider type

Statistical Analysis of Provider Differences

Chi-square analysis revealed statistically significant differences in melanoma diagnostic accuracy among the four provider types ($\chi^2 = 112.84$, df = 3, $p < 0.001$). Cramer's V was 0.094.

Pairwise comparisons using Fisher's exact test showed the following results: MDs versus DOs ($p = 0.0009528$), MDs versus NPs ($p = 0.005557$), MDs versus PAs ($p < 2.2 \times 10^{-16}$), and DOs versus NPs ($p = 0.7766$). The comparisons between MDs and DOs, MDs and NPs, and MDs and PAs were statistically significant ($p < 0.05$). The comparison between DOs and NPs was not statistically significant.

DISCUSSION

In this large, recent retrospective study of 12,852 skin biopsies submitted to ROM, we found that only 13.41% resulted in a histopathologic diagnosis of melanoma. 74.4% of melanomas diagnosed were melanoma in situ, highlighting a diagnostic yield skewed toward early-stage disease. Among the remaining 86.6% of cases, the most frequent benign histopathologic diagnoses were dysplastic nevi and seborrheic keratoses. These findings highlight the low pretest probability of malignancy in most ROM-labeled biopsies.

Our findings raise important considerations regarding the use of ROM language in

pathology requisitions. The high percentage of melanoma in situ diagnoses in our cohort corresponds to national trends. Several large epidemiologic studies have documented steadily rising melanoma incidence in the United States without a corresponding decline in mortality.[6 7 12] While this disconnect may partly reflect advances in melanoma treatment,[13] the potential for overdiagnosis has raised concerns as it may adversely contribute to patient anxiety, overtreatment, and unnecessary use of healthcare resources.[14]

Previous studies have reported PPVs for lesions clinically suspected of melanoma, varying from 2.5% to 40%, with most recent studies favoring a PPV closer to 6%[15 16,17] For example, a 2015 by Soltani-Arabshahi et al. examined 2653 biopsies performed by 43 dermatology providers (faculty, residents, and mid-levels) at a single academic institution found an aggregate PPV of 6.5% without. In contrast, our study demonstrated a greater PPV of 13.41%, which still fall within the range of reported spectrum of the PPV of melanoma.

The observed PPV variability between previous studies could be due to multiple contributing factors. First, our cohort included a high proportion of dermatology-trained MDs and DOs (~65%), whose diagnostic accuracy exceed that of non-dermatology providers. Second, many of the dermatologists in our sample were private practice physicians, a group that has been less well represented in prior research and may intrinsically have a lower threshold to biopsy. Third, the widespread use of dermoscopy and improvement in dermatological medical education may increase diagnostic precision compared to earlier studies. Finally, differences in sample size and provider distribution may also contribute as our study encompassed a larger number of biopsies and a more diverse mix of providers than some prior reports, improving the robustness of our estimates.

Our findings also revealed significant variation in melanoma detection rates across provider types. MD dermatologists achieved the highest diagnostic yield (15.77%), while PAs, DOs, and NPs demonstrated significantly lower yields. These results align with prior studies suggesting that diagnostic accuracy is influenced by dermatology-specific training and experience. [18,19 20 21] To our knowledge, this is the first large-scale study to directly compare possible melanoma biopsy outcomes across such a broad spectrum of provider types. The higher yield observed by dermatologists may be attributable to greater reliance on dermoscopy, more specialized training in pigmented lesion assessment, and stricter biopsy thresholds. Nevertheless, though MD dermatologists outperformed other types of providers on average, the PPV of suspected lesions remain relatively low. This likely suggests the tendency for all providers to biopsy lesions with low pretest probability and airing on the side of diagnostic caution. These findings underscore the need for more standardized clinical criteria and decision-support tools to improve diagnostic precision and minimize unnecessary biopsies. Enhancing diagnostic accuracy may also benefit from target educational interventions. Together, these strategies could help balance early melanoma detection with the imperative to minimize overdiagnosis and overtreatment.

This study has several important limitations. First, it was conducted through a single dermatopathology laboratory, which may limit the generalizability of our findings. Although the laboratory receives specimens from a diverse range of providers across geographic regions, the majority originate from

community-based private dermatology practices. As such, our findings may not be generalizable to institutions with varying biopsy submission patterns. Second, the retrospective design limits our ability to assess causality or to understand the clinical reasoning underlying biopsy decisions. We also lacked detailed provider-level data including length of experience and routine use of dermoscopy which likely influence diagnostic accuracy. Third, we had limited demographic information on patient-level factors that may impact our diagnostic yield. Additionally, the absence of longitudinal follow-up prevents evaluation of long-term outcomes such as recurrence, overtreatment, or psychological burden associated with false-positive diagnoses.

CONCLUSION

In this large retrospective study of 12,852 skin biopsies, ROM language was frequently applied to low-risk lesions and has a relatively low PPV. Diagnostic yield varied significantly by provider type, with MD board-certified dermatologists outperforming other provider degree types. Standardized requisition practices and targeted provider education may help optimize diagnostic accuracy and increase the PPV when providers ask to ROM.

Conflict of Interest Disclosures: None

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