# Are En Face Frozen Sections Accurate for Diagnosing Margin Status in Melanocytic Lesions?

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## Abstract

*To assess the diagnostic accuracy of margin evaluation of melanocytic lesions using en face frozen sections compared with standard paraffin-embedded sections, we studied 2 sets of lesions in which en face frozen sections were used for analysis of surgical margins (13 from malignant melanomas [MMs] and 10 from nonmelanocytic lesions [NMLs]). Routine permanent sections were cut after routine processing. The slides were mixed and coded randomly. Fifteen dermatopathologists examined the cases separately. Margin status was categorized as positive, negative, or indeterminate. Kappa statistics were calculated per dermatopathologist and per case.*

*One case from each group was excluded because epidermis was not available in the routine sections. Of 330 evaluations (22 cases, 15 dermatopathologists), there were 132 diagnostic discrepancies (40.0%): 66 each for MM and NML (mean per case for both diagnoses, 6). In 9 instances (6.8%), the change was from positive (frozen) to negative (permanent) and in 43 (32.6%), from negative (frozen) to positive (permanent). There was poor agreement between frozen and permanent sections ($\kappa$ range per dermatopathologist, –0.1282 to 0.6615).*

*If permanent histology is considered the "gold standard" for histologic evaluation, en face frozen sections are not suitable for accurate surgical margin assessment of melanocytic lesions.*

Frozen sections are used widely in pathology and dermatopathology to provide a quick diagnosis for a variety of lesions. Some previous studies recommended using frozen sections for histologic differentiation between nevus and malignant melanoma (MM).[1] However, the method of freezing and cryostat cutting results in slides of a lower technical quality than those from formalin-fixed, paraffin-embedded tissue. Therefore, it may be more difficult to evaluate morphologic detail in frozen sections. Mainly for that reason, although several authors have advocated the use of frozen sections for the diagnosis of pigmented lesions, including lentigo maligna,[2-4] other authors have discouraged that method.[5,6]

In addition to the technical problems associated with freezing, the evaluation of frozen sections to determine surgical margin status in pigmented lesions of the head and neck is complicated because of the presence of scattered atypical melanocytes, secondary to actinic damage. Analysis of sections cut perpendicular to the surgical margin permits examination of any possible lesion in the center of the specimen and its relation to the surgical margin. In contrast, in en face sections (ie, sections cut parallel to the surgical margin), the detection of an isolated, atypical melanocyte may represent either lentigo maligna at the margin or just a background of sun-damaged skin.

We assess the diagnostic accuracy of margin evaluation of melanocytic lesions using frozen sections cut en face compared with using paraffin-embedded material.

## Materials and Methods

We selected 24 blocks from 23 cases from the files of the Department of Pathology, the University of Texas M.D.

Anderson Cancer Center, Houston, in which en face frozen sections had been used to examine the surgical margins. The specimens included MM (n = 13) and nonmelanocytic lesions (NMLs; n = 10) **Table 1**. Technical quality of the slides was not a criterion for selection, in order to use a sample representative of frozen-section slides routinely performed in our laboratory **Image 1**. All frozen blocks were thawed, routinely processed in paraffin, and stained with H&E. An assistant randomly coded all slides (frozen and paraffin-embedded sections). The code was not broken until after examination of all the slides.

The slides were reviewed by 15 dermatopathologists (V.G.P., Z.B.A., R.L.B., P.H.D., R.E., L.F., J.G., M.G.H., M.E.M., M.W.P., M.S.R., J.A.R., M.A.S., M.J.T., and C.R.S.) who have a special interest in pigmented lesions; all are members of the North American Melanoma Pathology Study Group. Each dermatopathologist indicated whether she or he routinely performed frozen sections. The panelists independently examined all cases without knowledge of clinical histories or previous diagnoses. The panelists did not know which paraffin sections corresponded to the frozen sections and did not know whether the specimen contained MM or NML. There was no discussion of diagnostic criteria before or after the examination of the slides. Margin status was categorized as positive, negative, or indeterminate.

The statistical analysis was performed by one of us (M.M.J., a biostatistician). A simple κ statistic, a measure of agreement, was computed for each dermatopathologist and for each case. Ninety-five percent confidence intervals for κ were computed. The null hypothesis of zero agreement (κ = 0) was tested against the 1-sided alternative hypothesis that the agreement is better than chance agreement. In addition, the hypothesis of equal κ coefficients for all 15 pathologists was tested. The κ coefficients and 95% confidence intervals for κ were computed for pathologists' experience level with frozen-section methods. The expected results were as follows: If there is complete agreement between the 2 frozen-section and permanent-section findings, then κ = +1. If observed agreement is greater than or equal to chance agreement, then κ = 0 or more. For most purposes, values of κ greater than 0.75 represent excellent agreement beyond chance values, between 0.40 and 0.74 represent fair to good agreement, and values below 0.40 represent poor agreement.[7] All analyses were performed using SAS software (SAS Institute, Cary, NC) at a significance level of $P$ less than .05.

## Results

Two cases (1 MM and 1 NML) were excluded from the study because epidermis was not available in the permanent sections. Therefore, 330 diagnoses were possible (22 cases × 15 dermatopathologists). Discrepancies in diagnoses between frozen and permanent sections were analyzed by case **Table 2** and by dermatopathologist **Table 3**. There were 132 discrepancies (40.0%), 66 for MM cases (mean per case, 6) and 66 for NML (mean per case, 6). From this total of 132 discrepancies, in 80 instances the dermatopathologist classified margin status as indeterminate in either frozen or paraffin sections. In 9 instances (6.8%), there was a change from positive margin in the frozen section to negative in the permanent section. In 43 instances (32.6%), the diagnosis was changed from negative in the frozen section to positive in the permanent section.

For NML, a majority of dermatopathologists correctly interpreted the sections as not containing MM. This resulted in slightly better agreement between frozen- and permanent-section diagnoses for the NML than for the MM cases (κ = 0.38 and κ = 0.13, respectively).

The differences between dermatopathologists who routinely studied frozen sections (mean, 9.3 discrepancies) and those who did not (mean, 8.4 discrepancies) were not statistically significant ($P$ = .91). Still, agreement among dermatopathologists from the former group was slightly better (κ = 0.34) than among dermatopathologists from the latter (κ = 0.26).

## Discussion

Several authors, mostly dermatologists who perform Mohs surgery, have advocated the use of frozen sections for analyzing melanocytic lesions.[3,4,8-10] The obvious advantage of

**Table 1**
**Clinicopathologic Features of Studied Material**

| Original Diagnosis | No. of Paired Blocks | Anatomic Location of Lesions (No. of Blocks) | Mean Patient Age (y) |
|---|---|---|---|
| Melanoma (lentigo maligna type) | 7* | Cheek (7) | 54 |
| Melanoma (other) | 5 | Lip (2), cheek (2), scalp (1) | 63 |
| Basal cell carcinoma | 6* | Forearm (3), ear (3) | 78 |
| Extramammary Paget disease | 4 | Groin (4) | 68 |
| Squamous cell carcinoma | 2 | Forehead (1), scalp (1) | 69 |

* Two cases of lentigo maligna type were incidental findings after reexcision of lesions for basal cell carcinoma.


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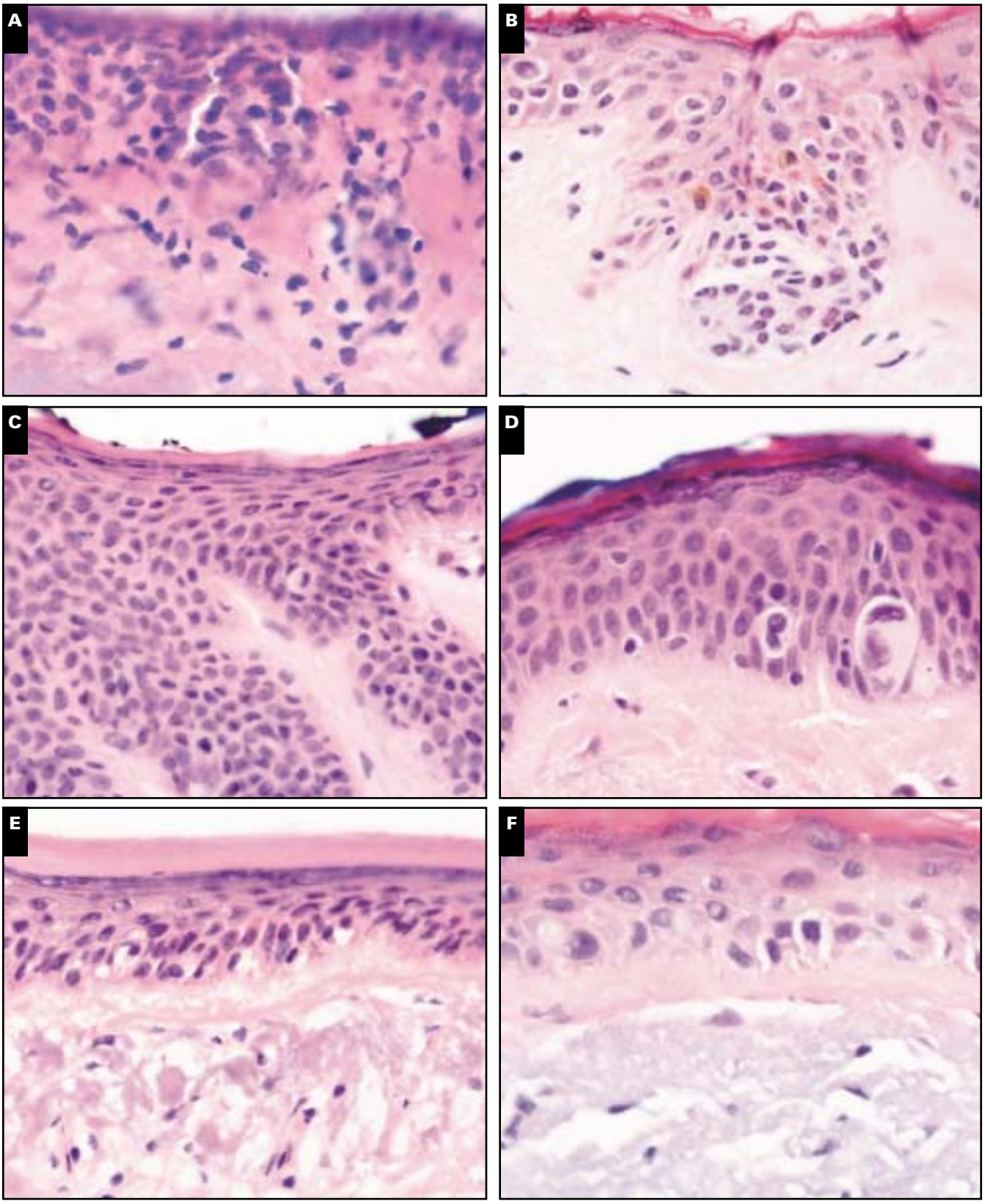


**Image 1** Comparison of frozen (**A, C, E**) and permanent (**B, D, F**) sections. **A**, Note the presence of a few clusters of small, hyperchromatic cells at the dermal-epidermal junction (H&E, ×400). **B**, In the corresponding permanent section, the presence of single and nests of atypical melanocytes are evident (H&E, ×400). **C**, Note a few single cells with possible pagetoid upward migration (H&E, ×400). **D**, In the corresponding permanent section, there are 2 small nests of frankly malignant melanocytes (H&E, ×400). **E**, Note the vacuolization of cells located in the basal layer (H&E, ×400). **F**, The corresponding permanent section shows only a few scattered, slightly enlarged melanocytes (H&E, ×400).




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**Table 2**
**Frozen-Section Diagnoses and Discrepancies in Frozen- vs Permanent-Section Diagnosis by Case***

| Case No. | Frozen Section Diagnosis | | | Changes in Diagnosis | | | | | | Total No. of Discrepancies |
|---|---|---|---|---|---|---|---|---|---|---|
| | + | – | ± | + to – | – to + | – to ± | ± to – | + to ± | ± to + | |
| 1 | 1 | 11 | 3 | 1 | 1 | 0 | 3 | 0 | 0 | 5 |
| 2 | 0 | 14 | 1 | 0 | 3 | 3 | 0 | 0 | 1 | 7 |
| 3 | 1 | 8 | 6 | 0 | 7 | 1 | 0 | 0 | 5 | 13 |
| 4 | 0 | 14 | 1 | 0 | 1 | 2 | 1 | 0 | 0 | 4 |
| 5 | 13 | 0 | 2 | 0 | 0 | 0 | 1 | 1 | 1 | 3 |
| 6 | 7 | 4 | 4 | 4 | 0 | 3 | 4 | 1 | 0 | 12 |
| 7 | 13 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8 | 6 | 6 | 3 | 0 | 4 | 2 | 1 | 1 | 0 | 8 |
| 9 | 12 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 3 |
| 10 | 3 | 8 | 4 | 1 | 1 | 3 | 0 | 1 | 2 | 8 |
| 11 | — | — | — | — | — | — | — | — | — | — |
| 12 | 2 | 8 | 5 | 0 | 8 | 0 | 0 | 0 | 5 | 13 |
| 13 | 1 | 6 | 8 | 1 | 0 | 0 | 7 | 0 | 0 | 8 |
| 14 | 0 | 11 | 4 | 0 | 2 | 3 | 3 | 0 | 0 | 8 |
| 15 | 1 | 12 | 2 | 0 | 12 | 0 | 0 | 0 | 2 | 14 |
| 16 | 0 | 11 | 4 | 0 | 1 | 1 | 3 | 0 | 0 | 5 |
| 17 | 0 | 14 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| 18 | 1 | 8 | 6 | 1 | 0 | 0 | 5 | 0 | 0 | 6 |
| 19 | 0 | 14 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| 20 | 1 | 10 | 4 | 1 | 0 | 0 | 3 | 0 | 0 | 4 |
| 21 | 0 | 14 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| 22 | 11 | 2 | 2 | 0 | 1 | 0 | 0 | 1 | 1 | 3 |
| 23 | 0 | 12 | 3 | 0 | 0 | 0 | 1 | 0 | 1 | 2 |
| 24 | — | — | — | — | — | — | — | — | — | — |
| Total changes | — | — | — | 9 | 43 | 22 | 32 | 5 | 21 | 132 |

+, positive; –, negative; ±, indeterminate.
* The first 3 columns indicate the total number of frozen-section diagnoses for each case. Overall $\kappa = 0.037$.

**Table 3**
**Discrepancies in Diagnosis per Dermatopathologist***

| Dermatopathologist No. | Total | + to – | – to + | – to ± | ± to – | + to ± | ± to + | Change to + | Change to – | Change to ± | Routine FS | κ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 10 | 0 | 0 | 2 | 5 | 2 | 1 | 1 | 5 | 4 | Yes | 0.2903 |
| 2 | 7 | 0 | 3 | 0 | 3 | 0 | 1 | 4 | 3 | 0 | Yes | 0.4296 |
| 3 | 6 | 0 | 3 | 1 | 1 | 0 | 1 | 4 | 1 | 1 | No | 0.4699 |
| 4 | 8 | 0 | 5 | 1 | 0 | 0 | 2 | 7 | 0 | 1 | No | 0.3868 |
| 5 | 14 | 1 | 2 | 6 | 3 | 1 | 1 | 3 | 4 | 7 | No | –0.1282 |
| 6 | 6 | 0 | 3 | 1 | 1 | 1 | 0 | 3 | 1 | 2 | Yes | 0.4634 |
| 7 | 11 | 2 | 2 | 1 | 4 | 0 | 2 | 4 | 6 | 1 | Yes | 0.1933 |
| 8 | 9 | 1 | 3 | 2 | 2 | 0 | 1 | 4 | 3 | 2 | Yes | 0.2944 |
| 9 | 7 | 1 | 4 | 0 | 0 | 1 | 1 | 5 | 1 | 1 | Yes | 0.4849 |
| 10 | 4 | 0 | 2 | 1 | 0 | 0 | 1 | 3 | 0 | 1 | No | 0.6615 |
| 11 | 10 | 0 | 2 | 1 | 4 | 0 | 3 | 5 | 4 | 1 | No | 0.2542 |
| 12 | 9 | 1 | 3 | 1 | 4 | 0 | 0 | 3 | 5 | 1 | Yes | 0.2471 |
| 13 | 9 | 0 | 5 | 3 | 1 | 0 | 0 | 5 | 1 | 3 | No | 0.3101 |
| 14 | 8 | 2 | 4 | 0 | 1 | 0 | 1 | 5 | 3 | 0 | Yes | 0.2903 |
| 15 | 14 | 1 | 2 | 2 | 3 | 0 | 6 | 8 | 4 | 2 | No | 0.0695 |
| Total | 132 | 9 | 43 | 22 | 32 | 5 | 21 | 64 | 41 | 27 | — | 0.2999 |

+, positive; –, negative; ±, indeterminate.
* "Change to" refers to the number of cases in which there was a change in diagnosis from frozen to permanent sections; "Routine FS" to whether the dermatopathologist routinely evaluated frozen sections.

using frozen sections is the ability to provide a quick diagnosis of the margin status, thus permitting completion of surgery on the same day. However, the quality of the sections usually is lower than that obtained with routinely processed, formalin-fixed tissue; therefore, the use of frozen sections has been discouraged by other authors.[5,6] Some advocates for Mohs surgery have proposed the use of a modified technique ("slow Mohs"), in which the wound is left open while the tissue margin is fixed, processed routinely, and reported as a regular dermatopathology specimen.[11-14]

Margin sections can be processed in 2 ways: perpendicular to the surgical margin and en face (or parallel) to the


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surgical margin. Both methods have advantages and disadvantages. En face sectioning may be the more common method, for both dermatopathologists and Mohs surgeons. En face sectioning permits the examination of the entire margin with a relatively low number of sections. However, sometimes it is difficult with en face sectioning to obtain a smooth, complete slice of tissue. Then, the incomplete section results in areas of the margin not available for evaluation. Also, en face sectioning does not permit the determination of the distance between the tumor and the margin; even if the margin is negative, the tumor may be just a few micrometers away (this statement may not apply to some Mohs surgery specimens because the surgeon can grossly measure the distance between one layer and the next). Finally, when dealing with melanocytic lesions of the head and neck, the identification of single, scattered melanocytes at an en face margin may represent lentigo maligna MM or sun-damaged skin with atypical melanocytes.

Perpendicular sections permit examining the morphologic features of the tumor, if present, in the frozen material and determining whether it extends to the margin and, if not, determining the distance from the tumor to the margin. Since this method permits direct comparison of the tumor and possible adjacent sun-damaged skin on the same slide, it may be particularly suitable for melanocytic lesions arising in sun-damaged skin. A drawback of the method of perpendicular sections is that the entire margin is not examined. Most pathologists and dermatopathologists will "breadloaf" the tissue in approximately 1- to 2-mm-thick slices; therefore, the margins in a portion of the specimen will not be examined unless the tissue block is cut through.

In the present study, we compared the degree of correlation of en face and permanent sections in cases of MM and NML when examined by dermatopathologists. We included NML because occasionally both MM and NML may be present in the same specimen; therefore, even if the original lesion being reexcised was a carcinoma, MM may be present in the reexcision specimen. This actually happened in 2 of the blocks selected for the present study.

Previous studies have analyzed the accuracy of frozen sections.[15-26] Fixation and processing likely affect the final size of the tissue for melanocytic lesions; in 1 series, Breslow thicknesses were at least 0.1 to 0.4 mm thinner in the frozen sections than in the paraffin-embedded sections,[27] although another study reported no significant differences.[28] Owing to these conflicting results and because Breslow thickness is still the most important prognostic factor for primary MM, the use of frozen sections should be discouraged for analyzing specimens that possibly contain MM.[29] In 1 series,[30] the authors recommended examining permanent sections and performing an immunohistochemical study with HMB45 to improve the detection of lentigo maligna at en face margins. Another study recommended the use of double-blade knives to obtain en face permanent sections.[31]

In our study, there was a general lack of agreement among dermatopathologists regarding correlation of frozen- and paraffin-section diagnoses (overall $\kappa = 0.29$; SE = 0.0375; range, –0.1282 to 0.6615). This discrepancy may be due to several factors. For changes in diagnosis from a negative to a positive margin (43 events), it is possible that MM cells were not present at the actual frozen-section margin but were present only after cutting deeper in the block to obtain permanent sections. Regardless, even though the actual margin was negative, the distance to the tumor (within micrometers) may be insufficient for adequate control of recurrence. Therefore, this relatively high number of discrepancies from a negative to a positive margin seems to support the current policy in most laboratories for processing the frozen-section material for routine histology and performing a diagnosis on that material as a quality control procedure.

Discrepancies involving the diagnosis of "indeterminate" on frozen sections and either positive or negative on permanent sections (53 events) may have been related to artifacts in the frozen section (eg, cautery, folding) or to how comfortable the dermatopathologist was in examining frozen sections. According to the participants, the slides provided were of standard quality. Also, we did not see any significant differences between dermatopathologists classifying themselves as "confident" on frozen sections and those who did not. A possible explanation is that the dermatopathologists in this study did not have the "pressure" of clinicians actually requesting them to evaluate the specimens while the patient is waiting under anesthesia.

In this study, even though the dermatopathologists did not know the previous diagnoses for the samples, there was slightly better agreement for identifying NML. Although not statistically significant, this finding suggests that dermatopathologists correctly identified sections as not containing MM slightly more easily than they identified the cases in which MM was present.

In our opinion, this study is relevant to the current situation of a substantial number of pathologists, those in academic practice and those in community practice, who encounter occasional requests from colleague clinicians to evaluate margins of melanocytic lesions. The justification for such requests is that, although clinicians know that the quality of frozen sections is lower than that of permanent sections, immediate evaluation of margins is needed to provide optimal patient care. However, as discussed, several authors have started to recommend temporarily covering the surgical wound and routinely processing the specimen in paraffin to permit evaluation of permanent sections the following day.[29,30] After the diagnosis is made, the clinician can decide whether additional tissue is necessary for further




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evaluation of the margins; if not, the wound then can be closed. Therefore, it seems that most cases may be treated in such a way, thus avoiding evaluation of frozen sections.

Our study further supports the opinion that the use of en face frozen sections should be discouraged in the evaluation of melanocytic lesions. In our opinion, the use of perpendicular sections or quick paraffin processing is a preferable option in most instances.

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