Title
Histopathologic synoptic reporting of invasive melanoma: How reliable are the data?

Journal
Cancer, 127(17)

ISSN
0008-543X

Authors
Taylor, Laura A
Eguchi, Megan M
Reisch, Lisa M
et al.

Publication Date
2021-09-01

DOI
10.1002/cncr.33612

Peer reviewed

HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2022 January 12.

Published in final edited form as:

Cancer. 2021 September 01; 127(17): 3125–3136. doi:10.1002/cncr.33612.

Histopathologic Synoptic Reporting of Invasive Melanoma: How Reliable Are the Data?

Laura A. Taylor, MD[1], **Megan M. Eguchi, MPH**[2], **Lisa M. Reisch, PhD**[3], **Andrea C. Radick, MS**[3], **Hannah Shucard, MS**[3], **Kathleen F. Kerr, PhD**[3], **Michael W. Piepkorn, MD**[4,5], **Stevan R. Knezevich, MD, PhD**[6], **David E. Elder, MB, ChB**[7], **Raymond L. Barnhill, MD**[8,9,10], **Joann G. Elmore, MD, MPH**[2]

[1]Division of Dermatology, Department of Medicine, University of Louisville, Louisville, Kentucky

[2]Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California

[3]Department of Biostatistics, University of Washington, Seattle, Washington

[4]Division of Dermatology, Department of Medicine, University of Washington School of Medicine, Seattle, Washington

[5]Dermatopathology Northwest, Bellevue, Washington

[6]Pathology Associates, Clovis, California

[7]Department of Pathology and Laboratory Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

[8]Department of Pathology, Curie Institute, Paris Sciences and Lettres Research University, Paris, France

[9]Department of Translational Research, Curie Institute, Paris Sciences and Lettres Research University, Paris, France

[10]Faculty of Medicine, University of Paris Descartes, Paris, France

Abstract

Corresponding Author: Joann G. Elmore, MD, MPH, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, 1100 Glendon Ave, Ste 850, Los Angeles, CA 90024 (jelmore@mednet.ucla.edu).

AUTHOR CONTRIBUTIONS

Laura A. Taylor: Conceptualization, methodology, and writing–original draft. **Megan M. Eguchi:** Visualization, data curation, formal analysis, and writing–original draft. **Lisa M. Reisch:** Conceptualization, methodology, project administration, investigation, and writing–original draft. **Andrea C. Radick:** Investigation, project administration, and writing–review and editing. **Hannah Shucard:** Investigation, project administration, and writing– review and editing. **Kathleen F. Kerr:** Supervision, project administration, visualization, and writing–review and editing. **Michael W. Piepkorn:** Conceptualization, methodology, resources, supervision, and writing– review and editing. **Stevan R. Knezevich:** Conceptualization, methodology, and writing–review and editing. **David E. Elder:** Conceptualization, methodology, supervision, and writing–review and editing. **Raymond L. Barnhill:** Conceptualization, methodology, supervision, and writing– review and editing. **Joann G. Elmore:** Conceptualization, methodology, investigation, project administration, funding acquisition, and writing– original draft.

CONFLICT OF INTEREST DISCLOSURES

David E. Elder reports royalties from Wolters Kluwer and consulting fees from the National Institutes of Health and Myriad Genetics as well as payments for expert testimony. Joann G. Elmore reports other financial or non-financial interests in UpToDate. The other authors made no disclosures.

Additional supporting information may be found in the online version of this article.

BACKGROUND: Synoptic reporting is recommended by many guideline committees to encourage the thorough histologic documentation necessary for optimal management of patients with melanoma.

METHODS: One hundred fifty-one pathologists from 40 US states interpreted 41 invasive melanoma cases. For each synoptic reporting factor, the authors identified cases with "complete agreement" (all participants recorded the same value) versus any disagreement. Pairwise agreement was calculated for each case as the proportion of pairs of responses that agreed, where paired responses were generated by the comparison of each reviewer's response with all others.

RESULTS: There was complete agreement among all reviewers for 22 of the 41 cases (54%) on Breslow thickness dichotomized at 0.8 mm, with pairwise agreement ranging from 49% to 100% across the 41 cases. There was complete agreement for "no ulceration" in 24 of the 41 cases (59%), with pairwise agreement ranging from 42% to 100%. Tumor transected at base had complete agreement for 26 of the 41 cases (63%), with pairwise agreement ranging from 31% to 100%. Mitotic rate, categorized as $0/mm^2$, $1/mm^2$, or $2/mm^2$, had complete agreement for 17 of the 41 cases (41%), with pairwise agreement ranging from 36% to 100%. Regression saw complete agreement for 14 of 41 cases (34%), with pairwise agreement ranging from 40% to 100%. Lymphovascular invasion, perineural invasion, and microscopic satellites were rarely reported as present. Respectively, these prognostic factors had complete agreement for 32 (78%), 37 (90%), and 18 (44%) of the 41 cases, and the ranges of pairwise agreement were 47% to 100%, 70% to 100%, and 53% to 100%, respectively.

CONCLUSIONS: These findings alert pathologists and clinicians to the problem of interobserver variability in recording critical prognostic factors.

LAY SUMMARY:

- This study addresses variability in the assessment and reporting of critical characteristics of invasive melanomas that are used by clinicians to guide patient care.
- The authors characterize the diagnostic variability among pathologists and their reporting methods in light of recently updated national guidelines. Results demonstrate considerable variability in the diagnostic reporting of melanoma with regard to the following: Breslow thickness, mitotic rate, ulceration, regression, and microscopic satellites.
- This work serves to alert pathologists and clinicians to the existence of variability in reporting these prognostic factors.

Keywords

dermatopathology; interobserver variability; melanocytic skin lesions; melanoma; synoptic reports

INTRODUCTION

Rates of melanoma diagnosis continue to increase, and proper management is necessary to optimize outcomes.[1] With pathology reports serving as the primary means of dialogue between pathologists and clinicians, it is essential for reports to be clear, for diagnoses

to be reproducible, and for the synopsis to contain key information to guide staging and treatment.[2]

Variability among pathologists regarding documentation of the salient histologic features within melanocytic proliferations has been reported.[3,4] Although the literature has repeatedly shown that there is poor agreement in the overall classification of melanocytic lesions,[4–8] variability in the reporting of the Breslow thickness (BT), the mitotic rate (MR), and ulceration also contributes to disagreement among invasive melanoma cases.[9–12] The seventh edition of the American Joint Committee on Cancer (AJCC) guidelines used these criteria for histologic staging of invasive melanoma. In 2018, in the eighth edition, the AJCC guidelines for the staging of invasive melanoma changed, with BT and ulceration kept as essential criteria and with MR removed.[13–15] However, whether these changes have affected diagnostic concordance in the setting of invasive melanoma is yet to be shown.

Our prior work described considerable variability in BT reporting,[3] but agreement improved when 1.0 mm was approached, the cutoff point of the AJCC's seventh edition separating T1 lesions from T2 lesions. Currently, T1 lesions are still defined as having a depth of ≤1.0 mm, but instead of ulceration and MR being used to differentiate T1a and T1b stages, T1a lesions are now defined as being <0.8 mm without ulceration, and T1b lesions are defined as being <0.8 mm with ulceration or 0.8 to 1.0 mm, regardless of ulceration. We previously showed that disagreement in the reporting of MR was the primary factor in staging discordance based on AJCC seventh edition criteria,[3] and we postulated an improvement in staging reproducibility with the removal of MR from the eighth edition of the AJCC staging criteria guidelines. This article serves to assess variability in evaluating and reporting these and other key prognostic factors with the updated AJCC staging criteria.

Pathologists' reporting practices vary. Although many use detailed synoptic reports, clinical practice is not universally standardized, and there is inadequate research characterizing best practices for reporting prognostic factors of melanoma. Although MR is no longer required as a staging criterion, many clinicians (supported by national guidelines) continue to consider MR and other synoptic prognostic factors, such as regression and lymphocytic host response, to be clinically relevant in a pathology report.[15,16] This study investigates the frequency of synoptic report utilization and also the consistency of the information detailed by pathologists for invasive melanoma.

MATERIALS AND METHODS

Slide Set Development

Melanocytic skin lesions biopsied from patients 20 years old or older were obtained from Dermatopathology Northwest, a pathology practice in Washington State. Shave, punch, and excisional biopsies were included, whereas consultative cases and re-excisions were excluded. A panel of 3 experienced pathologists (D.E.E., R.L.B., and M.W.P.) independently reviewed slides for each patient case, and this was followed by a consensus meeting using a modified Delphi approach.[17] The consensus panel identified 3 sequential cuts for each case that matched the consensus diagnosis in case of breakage, loss, or fading.

Cases ranging from benign to invasive were divided into 5 slide sets of 18 cases for use in the Reducing Errors in Melanocytic Interpretations (REMI) study. Slide sets were allocated with a randomization routine that balanced sets with respect to Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis classifications I to V,[18] prior interpretive variability, and level of diagnostic difficulty on the basis of assessments from participating dermatopathologists in the earlier Melanoma Pathology (M-Path) study.[4]

All procedures were compliant with the Health Insurance Portability and Accountability Act, and approval was obtained from the institutional review boards of the Fred Hutchinson Cancer Research Center (9551) and the David Geffen School of Medicine at the University of California Los Angeles (17–001881).

Participant Recruitment

Potential participants were recruited from all US states except for 10 states recruited in our earlier M-Path study: California, Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, Utah, and Washington. A list of potential participants (ie, board-certified in dermatopathology with available email addresses) was generated from Direct Medical Data, LLC, databases and randomly ordered. Potential participants were contacted by email (maximum of 3 attempts), which was followed by telephone calls (maximum of 2 attempts) and postal mail (1 attempt) to verify eligibility. The eligibility criteria were as follows: they were currently practicing in the United States, were board-certified and/or fellowship-trained in dermatopathology, had interpreted melanocytic skin biopsies within the previous year, and were expected to continue interpreting melanocytic skin lesions for the next 2 years. Eligible dermatopathologists were invited to enroll and to complete an online survey of demographic and clinical practice characteristics[19] between July 2018 and September 2019; it included the question “How often do you provide a synoptic report for melanoma cases?” with possible responses of “always,” “sometimes,” and “never.”

Slide Set Interpretations

Participants were randomized to receive 1 of the 5 sets of 18 melanocytic skin lesion cases. Participants chose a convenient 1-week period for their slide set interpretations. Using an online histology form, participants reported diagnoses, histological prognostic factors, treatment suggestions, and the perceived prognosis for each case. The Likert response scale for prognosis ranged from 1 (poor prognosis) to 6 (excellent prognosis). Dermatopathologists were instructed that the tissue section on each glass slide was representative of the lesion as a whole, the lesion extended to the edge of the sample, and thus the margins were to be considered positive. When participants diagnosed a case as invasive melanoma, they were asked to assess additional pathological factors in a synoptic report format: BT, ulceration, MR, lymphovascular invasion, perineural invasion, microscopic satellites, regression, and tumor transected at the base. BT, rounded to the nearest 0.1 mm, was dichotomized for analysis at the AJCC eighth edition threshold of <0.8 mm versus ≥ 0.8 mm. MR was categorized for analysis as $0/mm^2$, $1/mm^2$, or $\geq 2/mm^2$. Available responses for tumor transection were “no”, “yes, focally transected,” and “yes, broadly transected.” Responses for the remaining prognostic factors included “present”, “not identified,” and “cannot be determined.”

Data collection occurred between August 2018 and December 2019. Each slide set was interpreted by 29 to 32 dermatopathologists. At the study midpoint, because of fading of the slides from light exposure over time, all slides were replaced with the sequentially cut slides. The frequencies of the synoptic report prognostic factor responses were compared before and after the slide switch.

Analytic Plan

Because our objective was to examine variability in the synoptic reporting of prognostic factors of invasive melanomas, we confined the statistical analysis to 41 cases interpreted by both the consensus panel and at least 2 REMI study participants as invasive melanomas. According to consensus diagnoses, these were either pT1a cases (n = 32) or pT1b cases (n = 9; AJCC, eighth edition).

For each prognostic factor, we identified cases with complete agreement among all participants interpreting the case versus any disagreement among participants interpreting the case. For each case, we calculated the pairwise agreement as the proportion of pairs of responses that agreed, where paired responses were generated by the consideration of all unique pairs of 2 reviewers who interpreted the case. For example, the fewest number of reviewers per case was 4, which generated 6 unique pairs of reviewers; the maximum number of reviewers per case was 32, which generated 496 unique pairs. We chose pairwise agreement as our metric because it summarizes an easily interpretable quantity: if 2 reviewers independently interpret a case, what is the probability that their results are concordant? In contrast, metrics such as κ statistics are measures of agreement that are corrected for chance agreement and do not have a straightforward interpretation.

For the analysis of pathologist-reported prognosis, we dichotomized the 6-point scale into poor prognosis (ratings of 1–3) and good prognosis (ratings of 4–6). We estimated the relative risk of a poor prognosis based on each synoptic reporting factor by using a log-binomial model with generalized estimating equation methodology to account for clustered responses by participants. Because of the clinical importance of BT, we stratified analyses on the basis of the BT threshold of 0.8 mm before examing the effects of other prognostic factors. There were no other covariates in the regression model, so the relative risk estimates were unadjusted. Hypothesis testing results with $P < .05$ were considered statistically significant, and all analyses were completed with SAS 9.4 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Participants and Cases

Of 226 eligible responding dermatopathologists, 160 consented and completed the online survey (a 71% response rate), and 151 of these 160 dermatopathologists continued the study and completed slide set interpretations (Fig. 1). All 151 participants contributed interpretations to the 41 selected invasive melanoma cases. Table 1 summarizes physician demographics, training, and experience. All but 1 participant was board-certified in dermatopathology, and that participant was fellowship-trained in dermatopathology and,

therefore, eligible to participate. Eighteen participants (12%) had been interpreting melanocytic skin lesions for 1 to 4 years, 38 (25%) had been for 5 to 9 years, 64 (42%) had been for 10 to 19 years, and 31 (21%) had been for 20 years or more. Of the 151 participants, 142 (94%) responded that they always provided synoptic reports for melanoma cases.

The patient age distribution of the 41 cases was 16 cases aged 20 to 49 years (39%), 17 cases aged 50 to 64 years (41%), and 8 cases aged 65 years or older (20%). The patient sex distribution was 22 females (54%) and 19 males (46%). The cases included 22 shave biopsies (54%), 15 punch biopsies (37%), and 4 excisional biopsies (10%). The most frequent biopsy site was the limbs, excluding digits (46%), which were followed by the torso (29%), head and neck (15%), and acral sites (10%).

Synoptic Reporting Factors

Table 2 summarizes case-level pairwise agreement among the participants. Although 29 to 32 pathologists interpreted each case, participants completed synoptic reporting factors only for interpretations in which they identified the case as invasive melanoma. The median number of pathologists interpreting each case as invasive melanoma was 17 (range, 4–32) for 701 total invasive melanoma interpretations.

Figure 2 displays the distribution of each synoptic report factor for each of the 41 cases. For dichotomized BT, there was complete agreement among all participants for 22 cases (54%): 20 had complete agreement on BT < 0.8 mm (top panel of Fig. 2, cases 1–18, 20, and 21), and 2 had agreement on BT ≥ 0.8 mm (top panel of Fig. 2, cases 40 and 41). There was disagreement among participants on dichotomized BT for the remaining 19 cases (46%). Figure 3 shows the distribution of the reported BT for each case. In 11 of the 19 cases with any disagreement with respect to the 0.8-mm threshold, the 25th percentile to 75th percentile of responses landed on the same side of the 0.8-mm threshold. For an example of a case with a high degree of variability in BT across participants, see Figure 4.

The numbers of cases with complete agreement on the synoptic factors and the ranges of pairwise agreement are shown in Table 2. For ulceration, there was complete agreement for 24 cases (59%), all of which were classified as no ulceration. Pairwise agreement ranged from 42% to 100% across the 41 cases. For tumor transected at base, there was complete agreement for 26 cases (63%; range of pairwise agreement, 31%−100%). For MR, there was complete agreement for 17 cases (41%; range of pairwise agreement, 36%−100%). For regression, there was complete agreement for 14 cases (34%; range of pairwise agreement, 40%−100%). Lymphovascular invasion, perineural invasion, and microscopic satellites were rarely reported as present, and the number of cases with complete agreement were 32 (78%), 37 (90%), and 18 (44%), respectively.

Except for MR, the distributions of synoptic factor responses were similar in interpretations completed before and after we replaced the original slides because of fading with sequentially cut slides. For MR, interpretations using the replacement slides were more likely to report ≥2/mm^2 than interpretations using the original faded slides (15% of interpretations using the replacement slides vs 7% of those using the original slides), and

this highlights the importance of optimal histology in accurately observing and recording this attribute (Supporting Table 1).

Prognosis

Figure 5 presents the distribution, stratified by BT threshold, of participant-reported prognosis estimates provided for the 701 total invasive melanoma interpretations. Corresponding relative risk estimates can be found in Table 3. Among all interpretations with BT < 0.8 mm, 21% were given a poor prognosis, whereas this value was 69% for interpretations with BT ≥ 0.8 mm (relative risk, 3.06; 95% CI, 2.46–3.80; $P < .001$). Among cases with BT < 0.8 mm, participants were 1.41 times more likely to report a poor prognosis, on average, across increasing categories of MR (95% CI, 1.11–1.78; P for trend = .004). Interpretations with MRs of 0/mm^2, 1/mm^2, and ≥2/mm^2 were paired with a poor prognosis 19%, 31%, and 50% of the time, respectively. Participants reporting the presence of any other synoptic reporting factor (transected at base, lymphovascular invasion, perineural invasion, or microscopic satellites), in comparison with absence, were 1.81 times more likely to report a poor prognosis (95% CI, 1.29–2.53; $P < .001$). Among cases with BT ≥ 0.8 mm, interpretations with regression were 1.36 times more likely (95% CI, 1.15–1.60; $P < .001$) to be assigned a poor prognosis (89%) than interpretations with no regression identified (65%).

DISCUSSION

Our study data afford an opportunity to compare pathologists' agreement in the synoptic reporting of invasive melanoma with the eighth edition of the AJCC guidelines, and they demonstrate continued striking variability in the histopathological reporting of melanoma. We did not find any such comprehensive study of synoptic reporting in our review of the literature.

Of the histopathologic prognostic factors studied, the greatest variability in reporting occurred for the assessment of regression (complete agreement among all participants for only 34% of cases). The prognostic and biological significance of regression per se remains controversial, and the latter result is not surprising because of the longstanding difficulty in devising objective and agreed-upon criteria for its recognition.[20–22] Despite its poor reproducibility, its presence in melanomas > 0.8 mm was considered an adverse prognostic factor by study participants. Lymphovascular and perineural invasion demonstrated rates of complete agreement among pathologists at 78% and 90%, respectively. In contrast, there was complete agreement for only 44% of cases on the presence of microscopic satellites, which is incorporated into the AJCC model as a lymph node (N) staging criterion and prognostic factor. In an attempt to simplify the definition of microscopic satellites in the AJCC's eighth edition, size and minimal distance from the primary melanoma were eliminated as criteria. Microscopic satellites are now classified simply as discontinuous adjacent or deep microscopic tumor deposits.[13,23] Although there was a low prevalence of microscopic satellites reported in this study (n = 2), there is still ongoing confusion as well as difficulty experienced by pathologists in recognizing true microscopic satellites, as demonstrated by much of the disagreement arising from participants stating that their

presence could not be determined. This difficulty is related to the rarity of microscopic satellites and their distinction from a discontinuous primary tumor, adnexal involvement, artifacts, and so forth.[24]

Although there was considerable variability in reporting BT, which was consistent with our earlier report,[3] responses tended to be concordant with respect to staging breakpoints. For the majority of cases, there was at least 80% agreement on the BT category with the 0.8-mm cutoff. Our previous study[3] indicated greater concordance with respect to BT when a slight difference in depth would change the stage and thus the potential recommendation for sentinel lymph node biopsy, but there were too few cases with BT in proximity to the 0.8-mm cutoff in the current study to draw definitive conclusions.

Although stage T1a melanomas have more favorable outcomes than thicker melanomas and are, therefore, not subject to official recommendations for sentinel lymph node mapping, 21% of T1a lesions in this study were still considered to have a less favorable prognosis by participating pathologists. On scrutiny of the data, participants were more likely to estimate a poor prognosis for T1a lesions when they were associated with increased numbers of mitotic figures. In this study, MR, categorized as 0, 1, or 2/mm^2, had complete agreement for only 17 of the 41 cases (41%). It is interesting that the detection of mitotic figures increased when freshly stained slides were substituted for slides that had faded during our study; this indicates the importance of optimal histology. Published evidence that MR is well established as a key prognostic factor[25,26] and marker of tumor proliferation in melanoma signifies that the continued reporting of MR by pathologists is of great importance even though its removal as a staging criterion from the AJCC's eighth edition has brought about more reliable and reproducible staging. However, the removal of MR potentially could result in a failure to capture an important subset of cases that may require additional monitoring. In support of this, National Comprehensive Cancer Network guidelines and other guidelines[15–16,27] state that T1a melanomas with multiple mitoses may be considered for sentinel lymph node staging.

Despite the clinical importance of the aforementioned prognostic factors, they are often not recorded in a consistent manner in melanoma synoptic reports. A study of primary invasive melanoma reports in the New South Wales cancer registry between 2006 and 2007 found that only half included all the pathologic information necessary to properly stage the patient.[28] Additionally, the method of reporting was strongly associated with the completeness of the report, with structured synoptic formats being more complete than descriptive ones.[28–30] The importance of structured and clear reporting has been documented 32 of 33 studies).[33] Research suggests that templated pathology reports are more consistently complete and easier for clinicians to interpret.[34]

The 2019 American Academy of Dermatology guidelines for the management of primary cutaneous melanoma assign a grade A recommendation (essential) to MR inclusion in pathology reporting alongside BT and ulceration.[16] Grade B recommendations (not essential but useful) include level of invasion (Clark level), microsatellites, angiolymphatic invasion, histologic subtype, regression, and tumor-infiltrating lymphocytes; grade C recommendations (not essential but possibly useful) include ancillary molecular studies

in equivocal melanocytic neoplasms, neurotropism/perineural invasion, and clinical information. The guidelines also recommend against testing for mutations in the absence of metastatic disease or participation in a study.[16] Both MR and regression raised concern for worse outcomes among study participants, and this provides further support for their inclusion in histologic reports.

Limitations of the current study include the interpretation of a single slide (although participants were instructed to assume that the slide was representative), an inability to obtain second opinions and detailed clinical histories, and the context of a testing setting rather than a practice setting. Additionally, the low prevalence of features such as lymphovascular invasion, perineural invasion, and microscopic satellites in the selected cases provided fewer data points. Some participants may not have examined the cases with their normal standard of care with respect to Breslow measurements, for example, because actual patients were not affected. Additionally, microscopes were not standardized across participants, and it is possible that BT differences in the calibration of ocular micrometers produced different BT calculations. Although the lack of a gold standard presents a myriad of challenges to this study, it is representative of difficulties experienced in clinical practice, and as such, we would not characterize it as a limitation of the design, conduct, or execution of this study.

Strengths include a high response rate (71%) among invited nationwide dermatopathologists and a low attrition rate once they were enrolled. Additionally, unlike our earlier study, which recruited general pathologists,[3] participants in this study were all experienced board-certified and/or fellowship-trained dermatopathologists. This permitted us to evaluate synoptic reporting data among those most experienced in the field. Finally, our study design permitted a review of independent interpretations of the same glass slides among study participants, and all reported cases herein were determined to be invasive melanomas by an experienced consensus panel.

In summary, our results demonstrate considerable variability in the diagnostic synoptic reporting of melanoma with the use of the eighth edition of the AJCC criteria. Despite the updated criteria, diagnostic discordance remains an issue of concern. In particular, we observed inconsistent evaluations of key staging and prognostic histopathological factors: BT, MR, ulceration, regression, and microscopic satellites. Our work serves to alert pathologists and clinicians alike to the current problem of interobserver variability in reporting these critical factors, which are requisite to the optimal management of patients with melanoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING SUPPORT

This study was supported by grant R01 CA201376 from the National Institutes of Health/National Cancer Institute with additional support from the National Institutes of Health/National Center for Advancing Translational Sciences (UL1 TR002319) and the National Cancer Institute (Cancer Center grant P30 CA015704). The National Cancer Institute had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the

report; or in the decision to submit the article for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We thank the study participants for their commitment to improving clinical care in dermatopathology. We also thank Paul Litwin (Collaborative Data Services, Fred Hutchinson Cancer Research Center) for the development of the Reducing Errors in Melanocytic Interpretations web platform.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975–2016 National Cancer Institute; 2019. 1992;27(pt 1):741–749.
2. Nurdjaja V, Yozu M, Mathy JA. Essential components of melanoma histopathological reporting: the surgical oncologist's perspective. J Skin Cancer 2018;2018:9838410. [PubMed: 29854464]
3. Taylor L, Hood K, Reisch L, et al. Influence of variability in assessment of Breslow thickness, mitotic rate and ulceration among US pathologists interpreting invasive melanoma, for the purpose of AJCC staging. J Cutan Pathol 2018;45:588–596. [PubMed: 29717800]
4. Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study. BMJ 2017;357:j2813. [PubMed: 28659278]
5. Gerami P, Busam K, Cochran A, et al. Histomorphologic assessment and interobserver diagnostic reproducibility of atypical spitzoid melanocytic neoplasms with long-term follow-up. Am J Surg Pathol 2014;38:934–940. [PubMed: 24618612]
6. Duncan LM, Berwick M, Bruijn JA, Byers HR, Mihm MC, Barnhill RL. Histopathologic recognition and grading of dysplastic melanocytic nevi: an interobserver agreement study. J Invest Dermatol 1993;100:318S–321S. [PubMed: 8440913]
7. Duray PH, DerSimonian R, Barnhill R, et al. An analysis of interobserver recognition of the histopathologic features of dysplastic nevi from a mixed group of nevomelanocytic lesions. J Am Acad Dermatol 1992;27(pt 1):741–749. [PubMed: 1430397]
8. Corona R, Mele A, Amini M, et al. Interobserver variability on the histopathologic diagnosis of cutaneous melanoma and other pigmented skin lesions. J Clin Oncol 1996;14:1218–1223. [PubMed: 8648377]
9. Colloby PS, West KP, Fletcher A. Observer variation in the measurement of Breslow depth and Clark's level in thin cutaneous malignant melanoma. J Pathol 1991;163:245–250. [PubMed: 2013827]
10. Knezevich SR, Barnhill RL, Elder DE, et al. Variability in mitotic figures in serial sections of thin melanomas. J Am Acad Dermatol 2014;71:1204–1211. [PubMed: 25239732]
11. Spatz A, Cook MG, Elder DE, Piepkorn M, Ruiter DJ, Barnhill RL. Interobserver reproducibility of ulceration assessment in primary cutaneous melanomas. Eur J Cancer 2003;39:1861–1865. [PubMed: 12932663]
12. Eriksson H, Frohm-Nilsson M, Hedblad MA, et al. Interobserver variability of histopathological prognostic parameters in cutaneous malignant melanoma: impact on patient management. Acta Derm Venereol 2013;93:411–416. [PubMed: 23306667]
13. Amin MB, Edge SB, Greene FL, Byrd DR, eds. AJCC Cancer Staging Manual 8th ed. Springer; 2017.
14. Elmore JG, Elder DE, Barnhill RL, et al. Concordance and reproducibility of melanoma staging according to the 7th vs 8th edition of the AJCC cancer staging manual. JAMA Netw Open 2018;1:e180083. [PubMed: 30556054]
15. Scolyer RA, Rawson RV, Gershenwald JE, Ferguson PM, Prieto VG. Melanoma pathology reporting and staging. Mod Pathol 2020;33(suppl 1):15–24. [PubMed: 31758078]
16. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2019;80:208–250. [PubMed: 30392755]
17. Carney PA, Reisch LM, Piepkorn MW, et al. Achieving consensus for the histopathologic diagnosis of melanocytic lesions: use of the modified Delphi method. J Cutan Pathol 2016;43:830–837. [PubMed: 27247109]

18. Piepkorn MW, Barnhill RL, Elder DE, et al. The MPATH-Dx reporting schema for melanocytic proliferations and melanoma. J Am Acad Dermatol 2014;70:131–141. [PubMed: 24176521]
19. Shucard H, Piepkorn MW, Reisch LM, et al. Dermatopathologists' experience with and perceptions of patient online access to pathologic test result reports. JAMA Dermatol Published online January 29, 2020.
20. Aung PP, Nagarajan P, Prieto VG. Regression in primary cutaneous melanoma: etiopathogenesis and clinical significance. Lab Invest Published online February 27, 2017.
21. Kang S, Barnhill RL, Mihm MC, Sober AJ. Histologic regression in malignant melanoma: an interobserver concordance study. J Cutan Pathol 1993;20:126–129. [PubMed: 8320356]
22. El Sharouni MA, Aivazian K, Witkamp AJ, et al. Association of histologic regression with a favorable outcome in patients with stage 1 and stage 2 cutaneous melanoma. JAMA Dermatol 2021;157:166–173. [PubMed: 33355600]
23. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:472–492. [PubMed: 29028110]
24. Wilmott J, Haydu L, Bagot M, et al. Angiotropism is an independent predictor of microscopic satellites in primary cutaneous melanoma. Histopathology 2012;61:889–898. [PubMed: 22716270]
25. Pinero-Madrona A, Ruiz-Merino G, Cerezuela Fuentes P, MartinezBarba E, Rodriguez-Lopez JN, Cabezas-Herrera J. Mitotic rate as an important prognostic factor in cutaneous malignant melanoma. Clin Transl Oncol 2019;21:1348–1356. [PubMed: 30783917]
26. Wat H, Senthilselvan A, Salopek TG. A retrospective, multicenter analysis of the predictive value of mitotic rate for sentinel lymph node (SLN) positivity in thin melanomas. J Am Acad Dermatol 2016;74:94–101. [PubMed: 26542815]
27. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17:367–402. [PubMed: 30959471]
28. Haydu LE, Holt PE, Karim RZ, et al. Quality of histopathological reporting on melanoma and influence of use of a synoptic template. Histopathology 2010;56:768–774. [PubMed: 20546342]
29. ley A, Patrawala S, Stoff B. Compliance with the College of American Pathologists protocol for melanoma in synoptic and non-synoptic reports: a cross-sectional study. J Am Acad Dermatol 2016;74:179–181. [PubMed: 26702801]
30. Karim RZ, van den Berg KS, Colman MH, McCarthy SW, Thompson JF, Scolyer RA. The advantage of using a synoptic pathology report format for cutaneous melanoma. Histopathology 2008;52:130–138. [PubMed: 18184262]
31. Lankshear S, Srigley J, McGowan T, Yurcan M, Sawka C. Standardized synoptic cancer pathology reports—so what and who cares? A population-based satisfaction survey of 970 pathologists, surgeons, and oncologists. Arch Pathol Lab Med 2013;137:1599–1602. [PubMed: 23432456]
32. Aumann K, Amann D, Gumpp V, et al. Template-based synoptic reports improve the quality of pathology reports of prostatectomy specimens. Histopathology 2012;60:634–644. [PubMed: 22276642]
33. Sluijter CE, van Lonkhuijzen LR, van Slooten HJ, Nagtegaal ID, Overbeek LI. The effects of implementing synoptic pathology reporting in cancer diagnosis: a systematic review. Virchows Arch 2016;468:639–649. [PubMed: 27097810]
34. Aumann K, Niermann K, Asberger J, et al. Structured reporting ensures complete content and quick detection of essential data in pathology reports of oncological breast resection specimens. Breast Cancer Res Treat 2016;156:495–500. [PubMed: 27059032]

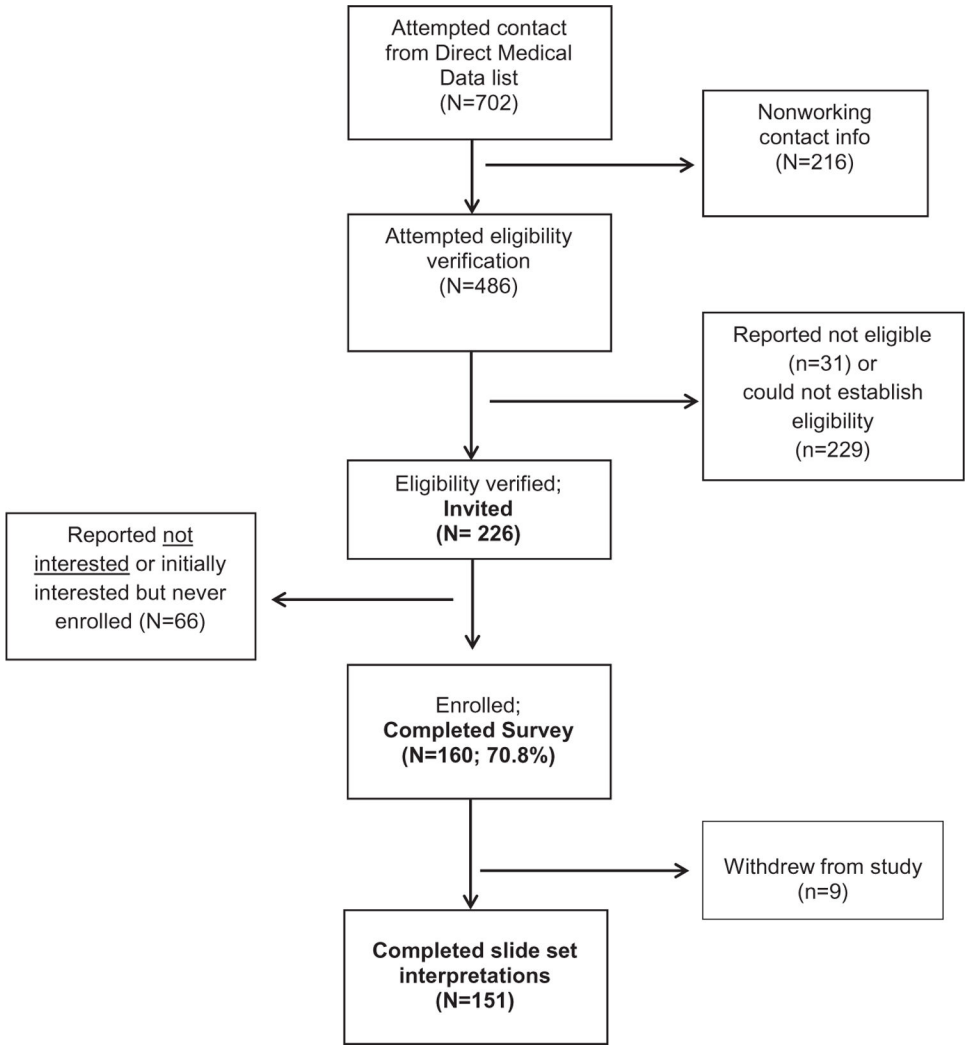

Figure 1.

Participant recruitment of dermatopathologists in the Reducing Errors in Melanocytic Interpretations study.

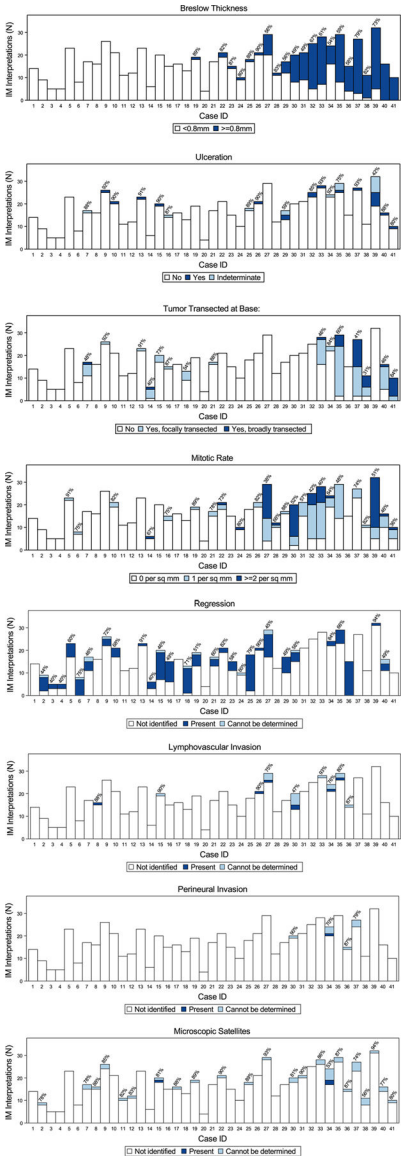

Figure 2.

Case-level variation in categorical synoptic reporting prognostic factors (see Fig. 3 for continuous Breslow thickness). Cases are ordered by the participant mean Breslow thickness, and the bar height represents the total number of IM interpretations per case. For cases without complete agreement, the proportion of pairwise agreement is reported. IM indicates invasive melanoma.

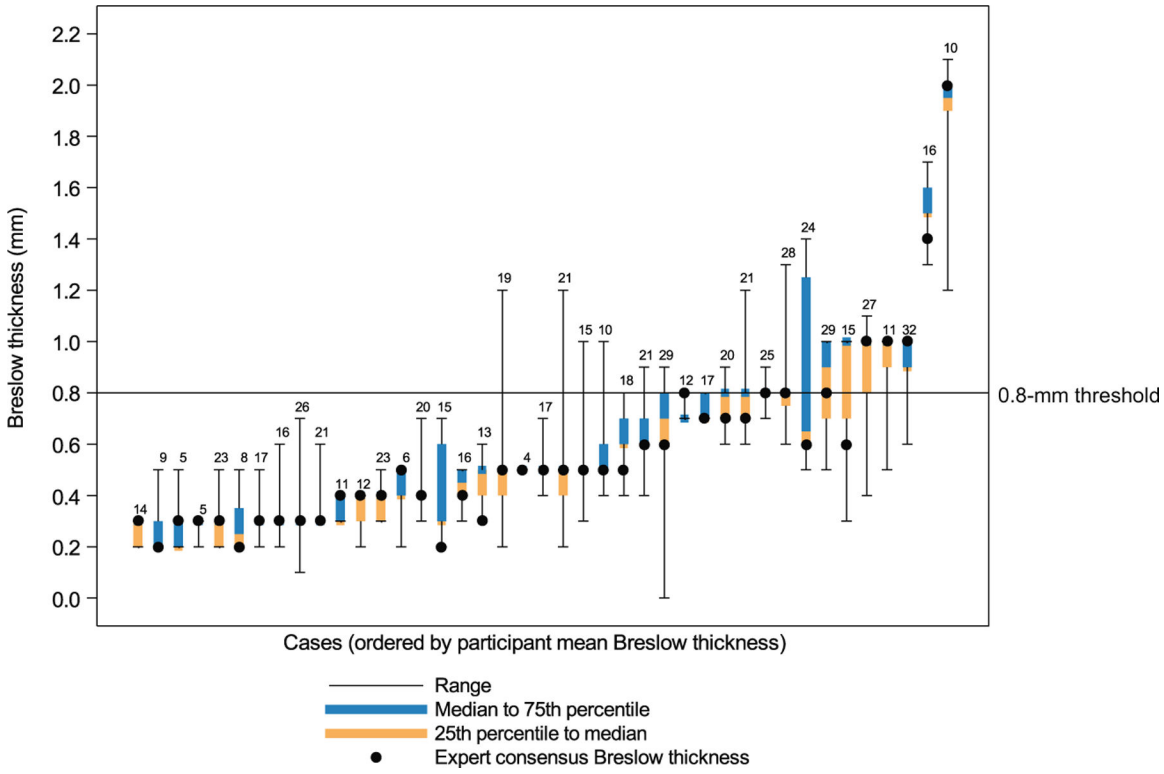

Figure 3.

Distribution of participant responses for Breslow thickness for each case. Cases are ordered by the participant mean Breslow thickness and correspond to the order of cases in Figure 2. The number of participants interpreting each case as invasive melanoma is displayed for each case (eg, 14 for the first case). Participants could report the Breslow thickness to the hundredth of 1 mm (0.01 mm). For all analyses, the participant-reported Breslow thickness was rounded to the nearest tenth of 1 mm (0.1 mm).

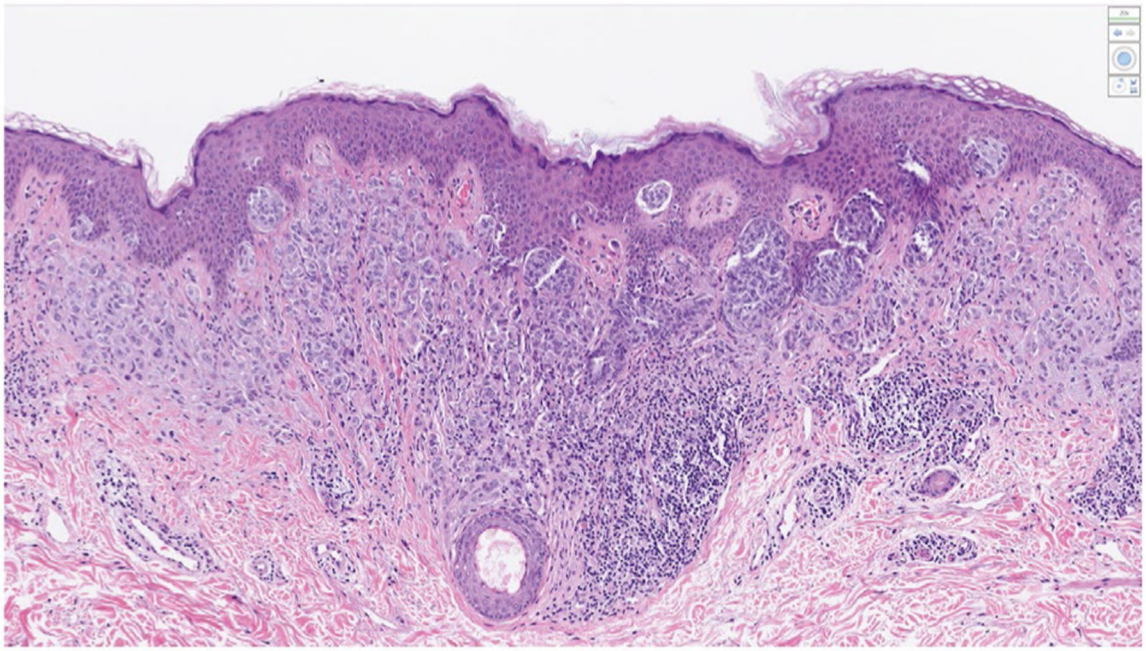

Figure 4.

Example of invasive melanoma with variability in Breslow thickness measurements. Among all possible pairs of interpretations of this case, there was only 49% agreement on dichotomized Breslow thickness (<0.8 mm vs ≥0.8 mm); this meant that there was high variability in the assigned histopathologic stage of this lesion. The advancing edge of the melanoma pictured is irregular and poorly defined, and this gives rise to several potential areas for measuring Breslow thickness. The presence of a hair follicle may lead to an incorrect, deeper measurement by some. Lastly, the presence of lymphocytes may make identification of the deepest aspects of the melanocytic proliferation difficult. The image has a resolution of 20×.

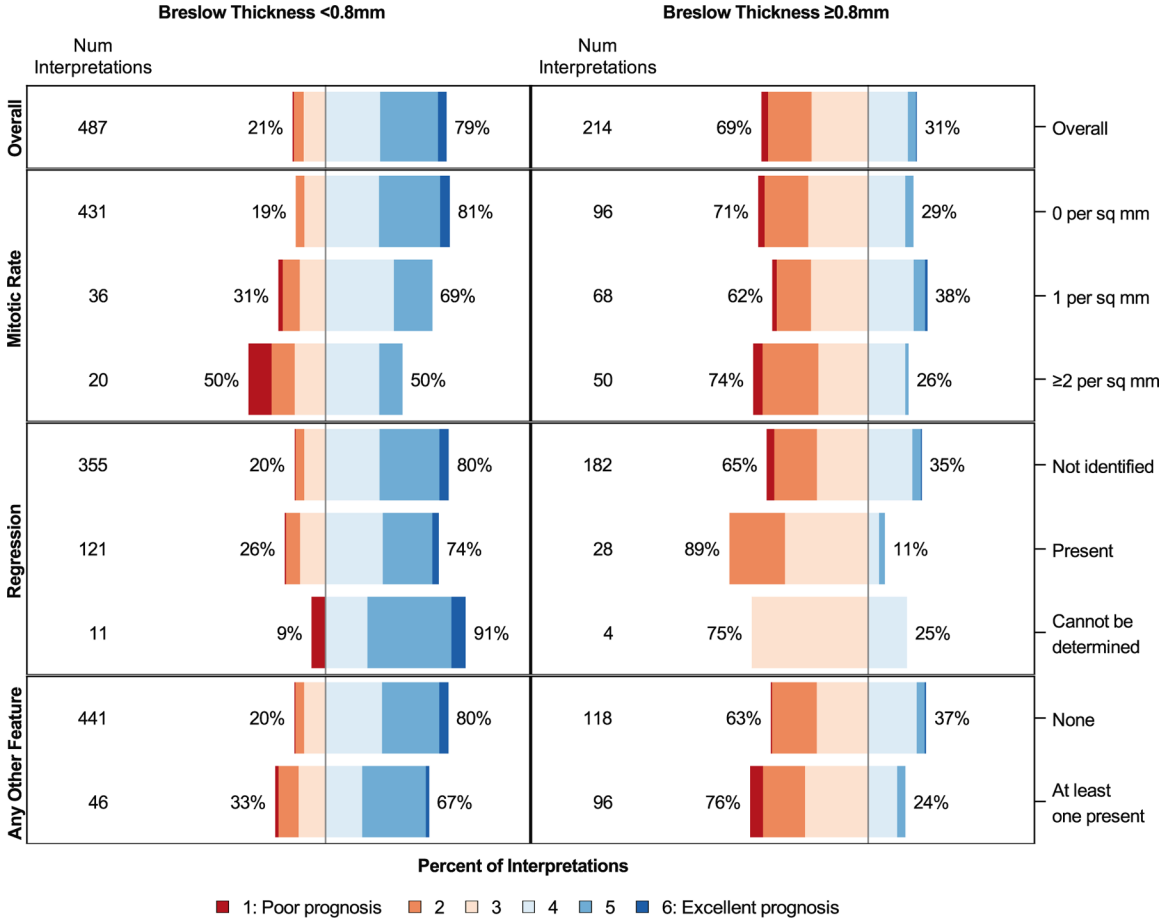

Figure 5.

Associations, stratified by Breslow thickness, between participant-reported prognosis and synoptic reporting factors. “Any other feature” includes transected at base, lymphovascular invasion, perineural invasion, and microsatellites.

TABLE 1.

Dermatopathologist Characteristics (N = 151)

Characteristic	Frequency (%)
Demographics	
Age	
<40 y	26 (17)
40–49 y	65 (43)
50–59 y	40 (26)
≥60 y	20 (13)
Sex[a]	
Male	103 (68)
Female	46 (30)
Training and experience	
Affiliation with academic medical center	
No	71 (47)
Yes, adjunct/affiliated clinical faculty	46 (30)
Yes, primary appointment	34 (23)
Residency (check all that apply)[b]	
Anatomic/clinical pathology	81 (54)
Anatomic pathology	27 (18)
Dermatology	51 (34)
Board certification (check all that apply)	
Dermatopathology	150 (99)
Anatomic pathology	108 (72)
Clinical pathology	77 (51)
Dermatology	50 (33)
Other	10 (7)
Fellowship and/or board-certified in dermatopathology	
Yes	151 (100)
Years interpreting melanocytic skin lesions	
1–4 y	18 (12)
5–9 y	38 (25)
10–19 y	64 (42)
≥20 y	31 (21)
% of caseload interpreting melanocytic skin lesions	
<10%	7 (5)
10%−24%	73 (48)
25%−49%	52 (34)
≥50%	19 (13)
How often do you provide a synoptic report for melanoma cases?	
Always	142 (94)
Sometimes	7 (5)

Characteristic	Frequency (%)
Never	2 (1)

[a]Two participants responded “prefer not to answer.”

[b]Three participants responded “other residency.”

TABLE 2.

Interpretations per Case and Pairwise Agreement Summarized Across 41 Cases

	Median (Range)	25th Percentile	75th Percentile
Total interpretations per case	17 (4–32)	12	21
Pairwise comparisons per case	136 (6–496)	66	210

	Pairwise Agreement, %			Cases With Any Disagreement, No. (%)	Cases With Complete Agreement, No. (%)
	Median (Range)	25th Percentile	75th Percentile		
Breslow thickness[a]	100 (49–100)	79	100	19 (46)	22 (54)
Ulceration	100 (42–100)	90	100	17 (41)	24 (59)
Transected at base	100 (31–100)	84	100	15 (37)	26 (63)
Mitotic rate[b]	82 (36–100)	67	100	24 (59)	17 (41)
Regression	79 (40–100)	51	100	27 (66)	14 (34)
Lymphovascular invasion	100 (47–100)	100	100	9 (22)	32 (78)
Perineural invasion	100 (70–100)	100	100	4 (10)	37 (90)
Microscopic satellites	90 (53–100)	83	100	23 (56)	18 (44)

[a] Responses for Breslow thickness were dichotomized as <0.8 mm versus ≥0.8 mm.

[b] Responses for mitotic rate were categorized as 0/mm^2, 1/mm^2, or ≥2/mm^2.

TABLE 3.

Relative Risk (Unadjusted) That Participant Reports Poor Prognosis by Synoptic Reporting Factor (701 Interpretations)

Prognostic Factor	Relative Risk (95% CI)	*P*
Overall		
Breslow thickness: ≥0.8 mm vs <0.8 mm	3.06 (2.46–3.80)	<.001
Breslow thickness < 0.8 mm		
Mitotic rate trend (0, 1, ≥2/mm^2)	1.41 (1.11–1.78)	.004
Regression: present vs not identified	1.21 (0.82–1.80)	.330
Regression: cannot be determined vs not identified	0.68 (0.19–2.44)	.551
Any other feature: present vs none[a]	1.81 (1.29–2.53)	<.001
Breslow thickness ≥ 0.8 mm		
Mitotic rate trend (0, 1, ≥2/mm^2)	0.98 (0.88–1.09)	.719
Regression: present vs not identified	1.36 (1.15–1.60)	<.001
Regression: cannot be determined vs not identified	1.07 (0.62–1.85)	.804
Any other feature: present vs none[a]	1.27 (1.05–1.54)	.013

[a]"Any other feature" includes transected at base, lymphovascular invasion, perineural invasion, and microsatellites.