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Tiered Somatic Variant Classification Adoption Has Increased Worldwide With Some Practice Differences Based on Location and Institutional Setting

A Study From the College of American Pathologists Molecular Oncology Committee

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• Context.—The 2017 Association for Molecular Pathology/American Society of Clinical Oncology/College of American Pathologists (CAP) tier classification guideline provides a framework to standardize interpretation and reporting of somatic variants.

Objective.—To evaluate the adoption and performance of the 2017 guideline among laboratories performing somatic next-generation sequencing (NGS).

Design.—A survey was distributed to laboratories participating in NGS CAP proficiency testing for solid tumors (NGSST) and hematologic malignancies (NGSHM).

Results.—Worldwide, 64.4% (152 of 236) of NGSST and 66.4% (87 of 131) of NGSHM participants used tier classification systems, of which the 2017 guideline was used by 84.9% (129 of 152) of NGSST and 73.6% (64 of 87) of NGSHM participants. The 2017 guideline was modified by 24.4% (30 of 123) of NGSST and 21.7% (13 of 60) of NGSHM laboratories. Laboratories implementing the 2017 guideline were satisfied or very satisfied (74.2% [89 of 120] NGSST and 69.5% [41 of 59] NGSHM), and the impression of tier classification reproducibility was high (mean of 3.9 [NGSST] and 3.6 [NGSHM] on a 5-point scale). Of nonusers, 35.2% (38 of 108) of NGSST and 39.4% (26 of 66) of NGSHM laboratories were planning implementation. For future guideline revisions, respondents favored including variants to monitor disease (63.9% [78 of 122] NGSST, 80.0% [48 of 60] NGSHM) and germline variants (55.3% [63 of 114] NGSST, 75.0% [45 of 60] NGSHM). Additional subtiers were not favored by academic laboratories compared to nonacademic laboratories ($P < .001$ NGSST and $P = .02$ NGSHM).

Conclusions.—The 2017 guideline has been implemented by more than 50.0% of CAP laboratories. While most laboratories using the 2017 guideline report satisfaction, thoughtful guideline modifications may further enhance the quality, reproducibility, and clinical utility of the 2017 guideline for tiered somatic variant classification.

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The increasing availability of next-generation sequencing (NGS) of cancers has led to an exponential increase in the amount and complexity of molecular data generated in clinical settings.1 To provide clinically useful reports of sequencing data, a consistent, comparable, and comprehensive framework for the interpretation of detected somatic variants is highly desirable. Expert interpretation of sequencing results can aid oncologists and pathologists in identifying actionable diagnostic, prognostic, and predictive mutations.2 The need for a standardized classification system for somatic cancer variants is reflected in the increasing number of databases that aid in the interpretation of variants and the establishment of molecular tumor boards at many institutions.3 For germline variants, a universal interpretation framework was established more than 10
years ago. 4.5 Before 2017, several attempts to establish somatic variant classification systems addressing the clinical utility of mutations had been developed, including algorithmic models using online databases and rule-based classification frameworks, but failed to lead to uniform adoption. 6-8

In early 2017 the joint consensus working group composed of representatives from the Association for Molecular Pathology (AMP), the American Society of Clinical Oncology (ASCO), and the College of American Pathologists (CAP), published a 4-tiered somatic variant classification system (hereafter referred to as the “2017 guideline”). 9 This system categorizes somatic variants according to their clinical significance for the tumor type tested, using evidence-based criteria: tier 1, variants with strong clinical significance; tier 2, variants with potential clinical significance; tier 3, variants of unknown clinical significance; tier 4, variants deemed benign or likely benign (Figure 1). 9

The CAP is a leading provider of proficiency testing. As such, the CAP is uniquely poised, through the use of supplemental questionnaires included in proficiency testing surveys, to assess clinical practice trends and assay performance. 10-14 The primary objective of this study was to assess the adoption and implementation of the 2017 guideline for variant classification and reporting of somatic variants by laboratories performing NGS tumor assays. A secondary objective was to assess modifications to the guideline recommendations used by laboratories and to evaluate suggestions for future revisions of the guideline.

Figure 1. Reprint of the 2017 Tier Guideline Classification categories. Reprinted from Li et al,9 Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. Journal of Molecular Diagnostics. 2017;19(1):4-23, with permission from Elsevier. Abbreviation: FDA, US Food and Drug Administration.

MATERIALS AND METHODS

Survey Design

A 19-question cross-sectional survey (“Tier Guideline Questions”) was designed to assess a responding laboratory’s implementation of, modifications to, and satisfaction with the 2017 guideline for classifying somatic tumor variants in solid tumors and hematologic malignancies (see supplemental Table 1, see supplemental digital content). If the 2017 guideline was not used by a responding laboratory, the survey sought to identify which other reporting system(s) was used, for what reasons the 2017 guideline had not been implemented, and future plans for implementation. A subset of the tier guideline usage questions had been included in previous surveys attached to proficiency testing material since 2016. These results served to identify trends in variant classification over time. All respondents were queried for suggested future modifications to the 2017 guideline. The survey was developed by members of the CAP Molecular Oncology Committee in collaboration with a biostatistician.

Survey Administration

The “Tier Guideline Questions” survey tool was included with the second mailing of the CAP’s Next-Generation Sequencing Solid Tumor (NGSST) and Next-Generation Sequencing Hematologic Malignancies (NGSHM) proficiency testing surveys, which were administered in August and October 2019, respectively.

Data Analysis

Surveys with duplicate or largely incomplete responses and missing pages were excluded. The demographic results for the survey respondents were obtained from the CAP demographics database. Statistical tests were performed with SAS 9.4 (SAS Institute, Cary, North Carolina) and R 3.6.2. A 1-sided Cochran-Armitage trend test was used for evaluation of changes in tier guidelines adoption over...
than .05 was considered statistically significant. For multivariate models that did not meet the model convergence criterion, the model was adjusted to only include the low frequencies. For multivariate models that did not meet the model convergence criterion, the model was adjusted to only include the low frequencies. For multivariate models that did not meet the model convergence criterion, the model was adjusted to only include the low frequencies. For multivariate models that did not meet the model convergence criterion, the model was adjusted to only include the low frequencies. For multivariate models that did not meet the model convergence criterion, the model was adjusted to only include the low frequencies. For multivariate models that did not meet the model convergence criterion, the model was adjusted to only include the low frequencies. For multivariate models that did not meet the model convergence criterion, the model was adjusted to only include the low frequencies.

Institution location was defined as a 2-level factor for domestic (US) and international laboratories. Institution type was a 4-level factor defined as independent/commercial reference laboratories, academic (university or teaching) hospital/medical center, nonacademic (university or teaching) hospital/medical center laboratories performing NGSST and NGSHM, while academic hospital/medical center laboratories accounted for 32.6% (77 of 236) of NGSST and 43.5% (57 of 131) of NGSHM respondents, respectively. Survey questionnaires were most likely to be completed by a laboratory professional in the role of laboratory director and/or molecular pathologist (61.4%, 143 of 233 for NGSST; 72.3%, 94 of 130 for NGSHM).

Implementation of Tier Classification Systems

The percentage of NGSST and NGSHM laboratories using a tiered classification approach steadily increased over time from 2016 to 2019 among the respondent laboratories (Figure 2). At the time of the latest survey in 2019, 64.4% (152 of 236) of NGSST and 66.4% (87 of 131) of NGSHM laboratories used any tiered somatic variant classification system. Of NGSST survey respondents using tiered classification systems, 84.9% (129 of 152) used the 2017 guideline, of which 68.2% (88 of 129) used the 2017 guideline as the sole system in their laboratory. Almost a third of the 129 laboratories (31.8%; 41) used the 2017 guideline in addition to another system with 36 of them using the 2015 American College of Medical Genetics (ACMG)/AMP germline classification (Figure 3, A).6 Of NGSHM survey respondents using tiered classification, 73.6% (64 of 87) used the 2017 guideline, with 75% (48 of 64) using it as the sole classification system. One-third (16) of the 48 laboratories used the 2017 guideline in addition to another system with 14 of them using the 2015 American College of Medical Genetics (ACMG)/AMP germline classification (Figure 3, B). Other reporting systems included the International Agency for Cancer Research system,7 the University Health Network of Toronto Tiering System,7 adapted versions of the ACMG/AMP guideline for germline variant reporting,5 disease-specific systems, the Belgium Laboratory Accreditation classification system of the Commission for Personlized Medicine,15 and laboratory-defined systems such as the Brigham and Women’s Hospital/Dana Farber Cancer Institute method.16

Tier classification of somatic variants is performed by a single person or multiple individuals, with most laboratories involving between 2 and 3 individuals (77 of 124, 62.1% for NGSST; 33 of 60, 55.0% for NGSHM; Table 1). Resolution of classification discordances within laboratories was obtained by team-based reviews (28.2%, 31 of 110 for NGSST; 32.7%, 17 of 52 for NGSHM), additional individual review (eg, laboratory director) (27.3%, 30 of 110 for NGSST; 25.0%, 13 of 52 for NGSHM), or a combination of these methods (Supplemental Table 2).
Utilization of the 2017 AMP/ASCO/CAP Tier Guideline

For clinical care, laboratories indicated that tier 1 variants were always included in reports (120 of 120, 100.0% for NGSST, Figure 4, A; 59 of 59, 100.0% for NGSHM, Figure 4, B) and tier 2 variants were reported by nearly all laboratories (118 of 120, 98.3% for NGSST and 59 of 59, 100.0% for NGSHM). In accordance with the 2017 guideline recommendations, 90.0% (108 of 120) of NGSST and 88.1% (52 of 59) of NGSHM laboratories reported tier 3 variants of unknown significance, with fewer laboratories reporting tier 4 benign/likely benign variants (24 of 120, 20.0% for NGSST; 10 of 59, 16.9% for NGSHM). For laboratories using the 2017 guideline for research reporting, the results were nearly identical to clinical reporting practices, with all laboratories reporting tier 1 variants (47 of 47, 100.0% of NGSST; 20 of 20, 100.0% of NGSHM), most reporting tier 2 (46 of 47, 97.9% of NGSST; 20 of 20, 100.0% of NGSHM) and tier 3 (42 of 47, 89.4% NGSST; 18 of 20, 90.0% NGSHM) variants, and fewer reporting tier 4 variants (13 of 47, 27.7% of NGSST, Figure 4, A; 3 of 20, 15.0% of NGSHM, Figure 4, B).

Somatic Tier Classification Practice Variations by Geographic Location for Solid Tumor Laboratories

Of respondents that adopted the 2017 guideline, virtually all domestic laboratories used it for clinical care (64 of 64, 100.0% NGSST; 39 of 40, 97.5% NGSHM), as well as virtually all international laboratories (57 of 58, 98.3% NGSST, Figure 5, A; 21 of 21, 100.0%, NGSHM, Figure 5, B). Use of the 2017 guideline for clinical trial testing was lower across domestic (35 of 64, 54.7% NGSST; 17 of 40, 42.5% NGSHM) and international (30 of 58, 51.7% NGSST; 9 of 21, 42.9% NGSHM) laboratories. Utilization of the 2017 guideline for research purposes was significantly higher among international laboratories than domestic laboratories for both NGSST (P = .009) and NGSHM (P = .005; Table 2). Domestic laboratories were more likely to use more than 4 tiers for variant interpretation for solid tumor studies (P = .03), while international laboratories were more likely to modify the 2017 guideline by using sub tiers (P = .04), and to use classification teams to resolve classification discrepancies (P = .005). These differences were not observed for NGSHM laboratories.

Current and Future Modifications to the 2017 AMP/ASCO/CAP Tier Guideline

Additions of sub tiers to the 2017 guideline were used by 24.4% (30 of 123) of NGSST and 21.7% (13 of 60) of NGSHM laboratories (Table 3). Most modifications were applied to tier 2 (29 of 30, 96.7% for NGSST; 11 of 13, 84.6% for NGSHM), followed by tier 1 (20 of 30, 66.7% for NGSST; 7 of 13, 53.8% for NGSHM) and tier 3 (9 of 30, 30.0% for NGSST; 4 of 13, 30.8% for NGSHM) variants. Of the sub tier options included in the survey, the most commonly added sub tier was “somatic variants with a US Food and Drug Administration (FDA)–approved drug in a different disease” (24 of 30, 80.0% for NGSST; 9 of 13, 69.2% for NGSHM), followed by “somatic variants that are part of criteria for a drug in a clinical trial” (21 of 30, 70.0% for NGSST; 8 of 13, 61.5% for NGSHM), “somatic variants with a biochemical effect, but no associated therapy” (17 of 30, 56.7% for NGSST; 7 of 13, 53.8% for NGSHM), and “somatic variants with no/poor evidence that the biomarker predicts response to this therapy (but have been studied in the past or considered based on biology)” (16 of 30, 53.3% for NGSST; 6 of 13, 46.2% for NGSHM).

All laboratories, regardless of their tier classification use, were queried for suggested modifications to future guideline updates (Table 4). Approximately a third of laboratories supported no further additions or sub tiers in future versions of the AMP/ASCO/CAP guideline (31.9% [38 of 119] of NGSST and 37.9% [22 of 58] of NGSHM respondents). Expanding the scope of the 2017 guideline to include variants to monitor disease (eg, variants that may be detected by sequential sequencing of peripheral blood samples, potentially at low allele frequencies, that may indicate disease persistence/progression or response to therapy) was particularly favored by 80.0% of NGSHM laboratories (48 of 60) and also supported by 63.9% of NGSST laboratories (78 of 122). Including pathogenic or likely pathogenic germline variants was particularly favored by NGSHM laboratories, but also supported by more than...
half of NGSST laboratories (63 of 114, 55.3% for NGSST; 45 of 60, 75.0% for NGSHM).

**Proposed Modifications to the 2017 AMP/ASCO/CAP Tier Guideline Vary by Institution Type**

Suggestions by NGSST laboratories to include subtier classifications were significantly influenced by institution type (Table 5). Independent/commercial reference laboratories and nonacademic hospitals/medical centers testing solid tumors were more likely to support subtiers for “FDA-approved drug in a different disease” and “criteria for clinical trial inclusion” than academic hospital/medical centers (P = .004 and P = .005, respectively). Similarly, 36.2% (21 of 58) of independent/commercial reference laboratories supported a subtier for “no/poor evidence for a biomarker predicting response to therapy (but have been studied in the past or considered based on biology),” while significantly fewer academic hospital/medical centers (4 of 40, 10.0%) and nonacademic hospital/medical centers (1 of 12, 8.3%) supported this proposed change (P = .02). No such significant differences were observed by institution type for NGSHM laboratories (Supplemental Table 3). Notably, 60.0% (24 of 40) of NGSST and 53.6% (15 of 28) of NGSHM academic hospitals/medical centers supported no modifications, while significantly fewer independent/commercial reference laboratories and nonacademic hospital/medical centers supported no subtier modifications for both NGSST (P < .001) and NGSHM (P = .02).

**Future Adoption of the 2017 AMP/ASCO/CAP Tier Guideline**

Of the survey participants who did not use the 2017 guideline at the time of the survey in 2019, 35.2% (38 of 108) of NGSST and 39.4% (26 of 66) of NGSHM laboratories planned to adopt the guideline (Supplemental Table 4). Approximately half of the laboratories not using the guideline were unsure about their implementation (51.9%, 56 of 108 for NGSST; 43.9%, 29 of 66 for NGSHM). Thirteen percent (14 of 108) of NGSST and 16.7% (11 of 66) of NGSHM respondents not planning to implement the 2017 guideline reported the following reasons: satisfaction with their current classification system (9 of 14 NGSST; 6 of 11 NGSHM), insufficiency of the 2017 guideline for clinical practice (3 of 14 NGSST; 1 of 11 NGSHM), and lack of reproducibility of tier classification (2 of 14 NGSST; 1 of 11 NGSHM). Other reasons included the following: the terms pathogenic, likely pathogenic, and variant of unknown significance were more intuitive for clinicians who may not be familiar with the 2017 guideline (3 responses); the laboratory only reports targeted hot spot mutations (1 response); the laboratory was required to use an FDA-approved reporting system (1 response); and the interpretation of detected variants was performed elsewhere (1 response).

**End-User Feedback**

Perceived reproducibility of variant classification using the 2017 guideline was assessed on a Likert scale (1 = low, 5 = high) and revealed a mean rating of 3.9 for 119 NGSST and 3.6 for 59 NGSHM laboratories (Figure 6, A). Slightly more NGSST respondents were very satisfied with the 2017 guideline (13 of 120, 10.8%), as compared to NGSHM laboratories (3 of 59, 5.1%). For NGSST and NGSHM, 74.2% (89 of 120) and 69.5% (41 of 59) of respondents, respectively, were “very satisfied” or “satisfied” with the 2017 guideline (Figure 6, B). No laboratories were “very dissatisfied” with the guideline. However, 3 NGSST (2.5%) and 2 NGSHM (3.4%) laboratories were “dissatisfied” with the 2017 guideline.

Laboratory-reported oncologists’ feedback on the use of the 2017 guideline was received by a minority of NGSST (53 of 120, 44.2%) and 27 NGSHM (27 of 58, 46.5%) laboratories. Positive (29 of 53, 54.7%) or mixed (positive...
and negative) feedback (24 of 53, 45.3%) represented all results for NGSST respondents (Figure 6, C). Feedback for NGSHM laboratories was slightly less positive (12 of 27, 44.4%), had a slightly larger proportion of mixed feedback (14 of 27, 51.9%), and 1 reported negative oncologist feedback (1 of 27, 3.7%). There were no significant differences between NGSST and NGSHM respondents for satisfaction scores and oncologists’ feedback.

Figure 4. Proportion of laboratories reporting tiers 1 to 4 of the 2017 Association for Molecular Pathology/American Society of Clinical Oncology/College of American Pathologists guideline on clinical and research reports. A, Solid tumors survey respondents. B, Hematologic malignancies survey respondents. Abbreviations: HM, hematologic malignancies; ST, solid tumors.

Figure 5. Use of the 2017 guideline for clinical reports, clinical trials, and research by domestic and international laboratories. A, Solid tumors survey respondents. B, Hematologic malignancies survey respondents. Abbreviations: HM, hematologic malignancies; ST, solid tumors.
DISCUSSION

Approximately 2 years following publication of the 2017 AMP/ASCO/CAP tier guideline for somatic variant classification, the CAP Molecular Oncology Committee aimed to assess the implementation and use of the 2017 guideline across an array of domestic and international laboratories subscribed to somatic NGS proficiency testing surveys. The results demonstrate that most laboratories used tier-based systems to classify and report somatic variants in both solid tumors and hematologic malignancies by the end of 2019.

### Table 2. Tier Classification Practices by Laboratory That Vary by Location

| Practice                                                                 | Solid Tumor, No. (%) | Hematologic Malignancies, No. (%) |
|-------------------------------------------------------------------------|----------------------|----------------------------------|
| Laboratory uses the 2017 AMP/ASCO/CAP guideline for the following purpose(s) (multiple responses allowed) |                       |                                  |
| Clinical care                                                          | 64 (100.0)           | 39 (97.5)                        |
| Clinical trials                                                        | 35 (54.7)            | 17 (42.5)                        |
| Research                                                               | 18 (28.1)            | 8 (20.0)                         |
| Other                                                                  | 0 (0.0)              | 1 (4.8)                          |
| How many tiers are used by your laboratory for the interpretation of somatic variants? | n = 78               | n = 55                           |
| 1–2                                                                    | 3 (3.8)              | 3 (5.5)                          |
| 3–4                                                                    | 48 (61.5)            | 34 (61.8)                        |
| ≥ 5                                                                    | 27 (34.6)            | 18 (32.7)                        |

### Table 3. Modifications to the 2017 AMP/ASCO/CAP Guideline in Practice

| Practice                                                                 | Survey, No. (%) |
|-------------------------------------------------------------------------|----------------|
| Has your laboratory modified the 2017 AMP/ASCO/CAP guideline by adding sub tiers? | 123            |
| Yes                                                                     | 30 (24.4)      |
| No                                                                      | 93 (75.6)      |
| Which tiers from the 2017 AMP/ASCO/CAP guideline has your laboratory modified to include sub tiers? (multiple responses allowed) | 30             |
| Tier 1 - Variants of strong clinical significance                       | 20 (66.7)      |
| Tier 2 - Variants of potential clinical significance                    | 29 (96.7)      |
| Tier 3 - Variants of unknown clinical significance                      | 9 (30.0)       |
| Tier 4 - Benign or likely benign variants                               | 3 (10.0)       |
| Which of the following sub tiers does your laboratory use? (multiple responses allowed) | 30             |
| Somatic variants with an FDA-approved drug in a different disease       | 24 (80.0)      |
| Somatic variants that are part of criteria for a drug in a clinical trial | 21 (70.0)      |
| Somatic variants with a biochemical effect, but no associated therapy   | 17 (56.7)      |
| Somatic variants with no/poor evidence that the biomarker predicts response to this therapy (but have been studied in the past or considered based on biology) | 16 (53.3)      |

Abbreviations: AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; FDA, US Food and Drug Administration.
monly (84.9% of NGSST and 73.6% of NGSHM) used the 2017 guideline. A little less than one-third of laboratories not using the 2017 guideline at the time of the survey planned implementation within the following 12 months. These findings parallel a recent study from Canada revealing 65.0% (22 of 34) of laboratories using the 2017 AMP/ASCO/CAP guideline with 27.3% (6 of 22) using a second interpretation guideline. In the study, 100% of survey participants supported endorsing a consensus guideline for somatic variant classification. However, there was no unanimous support for one set of guidelines, as only 38.0% deemed that the 2017 AMP/ASCO/CAP guideline should be mandatory and merely 52.0% thought that the 2017 guideline was sufficient, indicating that future modifications may be warranted.

The number of tiers used by laboratories over time appears to have shifted since the publication of the 2017 guideline. In the original publication, the authors had conducted a survey showing that most laboratories used 3 or 5 categories for classification. Our current survey results show that most laboratories use 4 tiers for interpretation and 3 tiers for reporting of somatic variants (omitting tier 4), reflecting the published 2017 guideline recommendation. For NGSST, domestic laboratories are more likely to use 5 or more tiers for the interpretation of somatic variants than international laboratories (Table 2), which may indicate adoption by domestic laboratories of alternative multiple tier systems other than the 2017 guideline. Additional differences between international and domestic tier utilization for research suggests that international laboratories may be using the 2017 guideline to qualify patients for research protocols.

Labs that had not yet or will not adopt the 2017 guideline cited the following reasons for nonadoption:

### Table 4. Proposed Modifications to the 2017 AMP/ASCO/CAP Tier Guideline

| Demographic | Survey, No. (%) | Solid Tumor | Hematologic Malignancies |
|-------------|----------------|-------------|-------------------------|
| Which of the following sub-tier does your laboratory support adding to future versions of the guideline? (multiple responses allowed) | n = 119 | n = 58 |
| Somatic variants with an FDA-approved drug in a different disease | 72 (60.5) | 31 (53.4) |
| Somatic variants that are part of criteria for a drug in a clinical trial | 66 (55.5) | 26 (44.8) |
| Somatic variants with a biochemical effect, but no associated therapy | 40 (33.6) | 21 (36.2) |
| Somatic variants with no/poor evidence that the biomarker predicts response to this therapy (but have been studied in the past or considered based on biology) | 27 (22.7) | 14 (24.1) |
| Other | 0 (0.0) | 1 (1.7) |
| None | 38 (31.9) | 22 (37.9) |

To expand the scope of the 2017 AMP/ASCO/CAP guideline, does your laboratory support the following modifications?

| Include variants to monitor disease | n = 122 | n = 60 |
|-----------------------------------|---------|-------|
| Yes | 78 (63.9) | 48 (80.0) |
| No | 16 (13.1) | 8 (13.3) |
| Unsure | 28 (23.0) | 4 (6.7) |

| Include pathogenic or likely pathogenic germline variants | n = 114 | n = 60 |
|---------------------------------------------------------|---------|-------|
| Yes | 63 (55.3) | 45 (75.0) |
| No | 22 (19.3) | 8 (13.3) |
| Unsure | 29 (25.4) | 7 (11.7) |

Abbreviations: AMP, Association for Molecular Pathology; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; FDA, US Food and Drug Administration.

### Table 5. Proposed Subtier Modifications from Solid Tumor Laboratories by Institution Type

| Proposed Future Subtier Classification for Somatic Variants | Independent/Commercial Reference Laboratory, No. (%) (n = 58) | Academic Hospital/Medical Center, No. (%) (n = 40) | Nonacademic Hospital/Medical Center, No. (%) (n = 12) | Other, No. (%) (n = 9) | P Value |
|------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------|---------------------|---------|
| FDA-approved drug in a different disease | 42 (72.4) | 15 (37.5) | 9 (75.0) | 6 (66.7) | .004 |
| Criteria for a drug in a clinical trial | 39 (67.2) | 12 (30.0) | 9 (75.0) | 6 (66.7) | .005 |
| Biochemical effect, but no associated therapy | 23 (39.7) | 12 (30.0) | 3 (25.0) | 2 (22.2) | .37 |
| No/poor evidence that the biomarker predicts response to this therapy (but have been studied in the past or considered based on biology) | 21 (36.2) | 4 (10.0) | 1 (8.3) | 1 (11.1) | .02 |
| None | 8 (13.8) | 24 (60.0) | 3 (25.0) | 3 (33.3) | <.001 |

Abbreviation: FDA, US Food and Drug Administration.

* Boldface indicates statistical significance.
satisfaction with their current reporting system, insufficiency of the 2017 guideline for clinical practice, lack of reproducibility, and lack of clinician familiarity. The latter being explained by terms such as pathogenic, likely pathogenic, and variant of unknown significance deemed more “intuitive” by respondents than the focus on clinical significance aimed at by the 2017 guideline. The results of our study would argue that some of these reasons may be unfounded, given the relatively high rate of self-reported reproducibility, laboratory satisfaction, and perceived oncologist feedback among laboratories that adopted the 2017 guideline.

Limitations of our results are that oncologist feedback, laboratory satisfaction, and reproducibility were only by report of laboratories using the 2017 tier guideline (by laboratory proxy, in the case of oncologists) and do not include comparison of other somatic classification systems. Since poor communication between laboratories and treating providers along with misunderstood reports can endanger patient safety, further surveys of oncologists’ understanding of tier classification systems would be useful. Additionally, given the relative novelty of the 2017 guideline, larger studies on its reproducibility are limited. A recent report showed that the median chance-corrected agreement (κ) among 15 individuals classifying the same variants was 0.32 and rose to 0.70 after individuals reviewed a database of evidence compiled on each variant during classification. However, at the time of that study only 3 of the 15 respondents had adopted the 2017 guideline in their clinical practice, which may have negatively impacted the results owing to unfamiliarity with the guideline.

Supporting continued adoption of the 2017 guideline is a recent study that showed that the transition to the 2017 guideline demonstrated high correlation with the previously implemented laboratory-developed classification system. Identified benefits of the 2017 guideline in this study were the clear and discretely defined literature sources and evidence criteria. While additional well-controlled studies on interobserver reproducibility in tier classification are required, efforts by multiple institutions to standardize and share clinical classification best practices and databases of genomic variants are ongoing.

An additional limitation of this survey is that it did not address the emerging field of quantitative or semiquantitative variant classification systems. Such interpretation and classification systems have been developed for constitutional diseases and incorporate quantitative or semiquantitative metrics for variants, based on empiric data, as reported for copy-number variant classification. Classification systems that use quantitative metrics to measure and classify a variant’s clinical impact aim to improve the quality, reproducibility, and utility of variant classification. In the future, improvements to objectivity and reproducibility may stem from the adoption of machine learning and artificial intelligence in tier classification systems, as has already been demonstrated for variant reporting.

Another limitation of this survey lies in the pool of respondents, which is restricted to laboratories subscribing to the CAP proficiency testing surveys. Naturally, subscribers might be more likely to adopt guidelines endorsed by the CAP, such as the 2017 AMP/ASCO/CAP guideline. While this survey assessed a substantial and likely representative number of laboratories, it did not necessarily reflect the practices of all laboratories performing somatic cancer variant testing in solid tumors and hematologic malignancies. The same limitation applies to international laboratories subscribed to the CAP proficiency surveys, which may be more likely to adopt a CAP-endorsed guideline, as
Modifications of the 2017 AMP/ASCO/CAP Tier Guideline

A minority of laboratories added specific sub tiers for classification of somatic variants, with most modifications applying to tier 2. Of the sub-tier options listed in the survey, “somatic variants with an FDA-approved drug in a different disease” and “somatic variants that are part of criteria for a drug in a clinical trial” were the most common modifications, both of which represent level C evidence according to the 2017 guideline classification. The other 2 listed sub-tier options (“somatic variants with a biochemical effect, but no associated therapy” and “somatic variants with no/poor evidence that the biomarker predicts response to this therapy”) represent level C and/or D evidence, and sometimes may fit better as tier 3 variants of uncertain significance depending on the strength of the evidence. Overall, if laboratories chose to use sub-tier modifications for the above-stated reasons, it is the opinion of the authors that the sub-tiers listed above are best situated under the tier 2 category to align with the 2017 guideline levels of evidence. Sub-tier were also added to tier 1, but only a single NGSHM laboratory provided a response specifying that they used a tier 1 sub-tier for germline pathogenic/likely pathogenic variants. Further studies would be needed to explore what modifications laboratories are using for tier 1 variants or whether laboratories were using the sub-tiers listed above under tier 1.

There was broad support among respondents to include variants used to monitor disease (especially among NGSHM respondents) and germline variants that are pathogenic or likely pathogenic. A guideline that specifically highlights variants amendable to molecular monitoring for progression and/or therapy response may better reflect growing practice trends of serial molecular monitoring, particularly for hematologic malignancies. Reporting of clinically significant germline variants (when known/confirmed germline) is already required by the 2017 guideline, for which following the ACMG/AMP germline guideline is recommended. Understanding which variants are germline versus somatic is important for multiple reasons including disease monitoring, predisposition to cancer, determining clonal hematopoiesis, and calculations for tumor mutational burden.

While there was broader consensus for suggested guideline modifications among laboratories for hematologic malignancies, there was significant disagreement between academic and independent/commercial laboratories for solid tumors. Academic laboratories did not support sub-tier modifications to the 2017 guideline, while nonacademic laboratories were likely to support adding sub-tier for NGSTT reporting. Whether preference for the 2017 guideline by laboratories in academic institutions is due to different reporting practices, communication with academic oncologists, or other factors, should be further explored.

CONCLUSIONS

Nearly two-thirds of domestic and international laboratories participating in the CAP NGS proficiency testing surveys have successfully adopted a tier-based classification system and most use the 2017 AMP/ASCO/CAP tier guideline exclusively or in combination with other guidelines. While the majority of laboratories view the 2017 guideline positively, most laboratories also favor targeted modifications including the addition of sub-tier for variants to monitor disease as well as germline variants. Future guideline modifications should consider the results in this survey to most adequately support laboratories’ needs in the rapidly evolving field of somatic variant reporting. Ideally, slight usage differences between classification of solid tumors and hematologic malignancies as well as the needs of academic and nonacademic practitioners should be taken into account in a future edition of the 2017 AMP/ASCO/CAP guideline.

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