Association for Pathology Informatics

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Association for Molecular Pathology
6120 Executive Blvd., Suite 700
Rockville, MD 20852

Subject: API's Response to the Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer

Dear Members of the AMP Guidelines Working Group,

I am writing in my dual capacity as a practicing pathologist and Co-Chair of the Association for Pathology Informatics to provide feedback on the draft updates to the "Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer." I commend the Working Group for its ongoing commitment to advancing the clarity and clinical utility of these recommendations in our rapidly evolving field. The effort to reaffirm and update the 2017 guidelines—with new recommendations addressing issues such as variant annotation, evidence classification, and the incorporation of cell-free DNA analyses—demonstrates the committee's dedication to both quality patient care and robust laboratory practice.

However, as someone involved in both the diagnostic and informatics aspects of pathology, I wish to raise several concerns that may impact both the quality of health care delivered and laboratory efficiency.

1. Reporting of Incidental Germline Findings (Updated Recommendation 4):

The draft strongly encourages laboratories to report pathogenic or likely pathogenic germline or presumed germline variants identified during somatic testing according to ACMG/AMP guidelines. This recommendation raises two critical issues:
• Training and Competency: Many practicing pathologists and laboratory professionals have limited formal training in interpreting incidental germline findings. The current proficiency among somatic laboratories in handling such variants is variable, and without enhanced competency training, there is a significant risk of misclassification or miscommunication of these findings.
• Patient Counseling and Impact: Only a minority of patients currently receive appropriate genetic counseling when incidental germline alterations are detected. This is particularly concerning given that such incidental findings may have profound implications for non-military patients (e.g., potential impacts on life insurance eligibility) and military personnel, for whom the Genetic Information Nondiscrimination Act does not offer comprehensive protection.

Suggestion: I recommend that the guidelines explicitly address these educational gaps. Consider incorporating a requirement for enhanced training modules and clear protocols for genetic counseling referrals. Moreover, the laboratory report should include a prominent disclosure explaining the limitations of tumor-only testing in determining germline status, along with recommendations for confirmatory germline testing where appropriate.

2. Impact on Clinical Care Quality:

While the draft guidelines aim to standardize variant interpretation across diverse tumor types, certain revisions may inadvertently increase the risk of misinterpretation by clinicians. For instance, the introduction of a fifth evidence classification level (Level E) for variants deemed oncogenic based solely on oncogenicity assessments—but lacking definitive clinical evidence—could lead to confusion if not accompanied by detailed operational definitions and illustrative examples.

Suggestion: The committee should consider providing supplemental documents or online tools that offer case-based examples and clear decision trees to aid laboratories and clinicians in categorizing Level E variants accurately.

3. Efficiency of Laboratory Workflows:

The proposed updates emphasize rigorous variant annotation (as seen in Recommendation 3) and the adoption of normalization tools (e.g., ClinGen Allele Registry). While these are undoubtedly valuable for consistency and clarity, they may also impose additional manual review steps that could extend turnaround times.

Suggestion: To balance thoroughness with efficiency, it would be beneficial for the guidelines to recommend validated, automated software solutions that integrate seamlessly into laboratory workflows. Additionally, establishing performance benchmarks and quality metrics for these tools would help ensure that the added complexity does not compromise operational efficiency.

4. Managed Variant and Variant Rescue Lists (Recommendation 7):

The recommendation for laboratories to curate managed variant lists to avoid false negatives—especially for variants with minor allele frequencies near laboratory cutoffs—has strong potential to improve diagnostic accuracy. However, it also demands significant informatics resources and ongoing curation efforts, which may not be uniformly available across all institutions.

Suggestion: The AMP might consider facilitating a centralized or shared resource model for these variant lists, thereby reducing redundancy and ensuring that smaller laboratories can benefit from expert-curated content without an undue resource burden.

5. Reporting in Liquid Biopsy and Hematologic Settings (Recommendations 8 and 9):

The draft guidelines appropriately extend the tiering system to variants detected via cell-free DNA analysis and to hematologic conditions such as clonal hematopoiesis. Nevertheless, distinguishing true tumor-derived variants from clonal hematopoiesis remains a significant challenge.

Suggestion: I encourage the committee to elaborate on methodologies for discerning the variant cellular compartment of origin, possibly by recommending confirmatory studies or additional bioinformatics filters. Clear guidelines in these contexts will enhance both the reliability of reported findings and their subsequent clinical interpretation.

6. Integration of Complex Biomarkers (Recommendation 10):

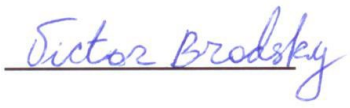
The concept of assigning mutational signatures and composite biomarkers (e.g., TMB, MSI, HRD) to guideline tiers is innovative and may provide a more comprehensive picture of tumor biology. Yet, the inherent complexity in calculating and interpreting these aggregated measures could create inconsistencies across laboratories.

Suggestion: It would be advantageous for the guidelines to detail standardized methods or reference tools for these complex assessments. This additional specificity would help maintain consistency in reporting and ensure that these biomarkers meaningfully contribute to clinical decision-making.

In conclusion, while I appreciate the thoughtful revisions introduced in the draft updates and the committee's drive to enhance both diagnostic accuracy and clinical relevance, addressing these concerns is vital. Enhancing training for incidental germline variant interpretation, ensuring efficient workflow integration, and providing robust support for emerging classifications and complex biomarkers will ultimately improve patient care and safeguard the quality and efficiency of laboratory practices.

Thank you for considering my feedback. I look forward to the opportunity to engage further with the Working Group as these important updates are refined.

Sincerely,



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