Put It on the Board

AMP offers recommendations for NGS germline variant confirmation

June 2023—The Association for Molecular Pathology and the National Society of Genetic Counselors released in May a report containing eight recommendations for next-generation sequencing germline variant confirmation.

The authors say in their article that the evidence-based consensus recommendations provide a framework for developing or refining individualized laboratory policies and procedures for orthogonal confirmation of germline variants detected by NGS.

The AMP clinical practice committee convened the NGS germline variant confirmation working group to assess current evidence and standardize orthogonal confirmation practices to help limit the reporting of false-positives. Kristy Crooks, PhD, associate professor and laboratory director at the University of Colorado Anschutz Medical Campus and chair of the working group, says orthogonal confirmation practices for germline variants may vary. "This new report provides recommendations for orthogonal confirmation practices that, in concert with existing guidelines, are designed to help promote standardization, transparency, and quality improvement among laboratories," she said in a May 18 news release.

She and her coauthors write, "Although the adoption of NGS technologies for clinical practice has been rapid, the development of specific guidelines related to such confirmatory testing has lagged, contributing to inconsistent policies between laboratories and raising potential patient safety concerns."

They based their recommendations on a review of the literature, a survey of clinical molecular genetics lab practices, expert consensus opinion, feedback from open public comment, and professional experience.

The eight recommendations, published online ahead of print in the *Journal of Molecular Diagnostics* (doi:10.1016/j.jmoldx.2023.03.012), are as follows:

1. Clinical laboratories offering germline testing using NGS should establish a written policy regarding orthogonal confirmation of NGS results.
2. Laboratories' orthogonal confirmation policy should be overseen and approved by a qualified and appropriately certified medical professional with training and experience in NGS.
3. Laboratories' confirmatory methods, platforms, and associated bioinformatics should be validated and maintained under appropriate regulatory oversight, as for other aspects of the test.
4. Laboratories' confirmatory methods should be orthogonal. Discrepant results between NGS and a confirmatory assay should be investigated and resolved, rather than accepting any one method to be always correct.
5. Laboratories should perform confirmatory testing for reported germline variants with significant clinical

implications, except for variant calls meeting technical criteria rigorously demonstrated to ensure high positive predictive value from NGS alone.

6. Laboratories should clearly articulate their specific policies, criteria, and methods regarding orthogonal confirmation in written materials readily available upon request.
7. Laboratories' clinical test reports should summarize orthogonal confirmation policy, and when exceptions to the policy are made, these should be clearly indicated.
8. Special considerations apply to certain NGS-based test types and findings.

USPSTF reaffirms latent TB screening in populations at increased risk

The U.S. Preventive Services Task Force reaffirmed its previously issued recommendation for latent tuberculosis infection screening in asymptomatic adults at increased risk.

The task force on May 2 issued its updated statement to continue the grade B recommendation for screening of persons who were born in or are former residents of countries with high TB prevalence and persons who live in or have lived in high-risk congregate settings. The recommendation replaces and is consistent with the task force's 2016 recommendation on LTBI screening.

Qiagen, which makes the QuantiFeron-TB Gold Plus, said in a May 3 news release that the reaffirmation helps ensure access to screening for insured patients in the U.S. who are at risk. The Affordable Care Act requires that insurers provide preventive services with an A or B recommendation at no cost.

The task force refers in its recommendation statement to the tuberculin skin test and the interferon-gamma release assays that are available for screening in the U.S. It also suggests that testing with IGRA may have advantages over the TST for those who have received a BCG vaccination or may be unlikely to return for TST interpretation.

"Stepping up screening is increasingly critical to achieve the ambitious End TB Strategy goals, especially in light of the setbacks in testing during the COVID-19 pandemic," Jenny Howard, Qiagen VP and head of the company's immune response franchise, said in the news release.