Editorial
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Integrating Rapid Lymphoma Next-Generation Sequencing Panel-Based Testing into Routine Genomic Diagnostics

Genomic testing has rapidly moved from research to routine diagnostics for hematological malignancies, transforming the classification and management of lymphoid neoplasms. Recently, WHO and International Consensus Classifications (ICC) have increasingly acknowledged the contribution of genetic features to the characterization of lymphoid neoplasms, where specific genomic alterations can help diagnose selected entities [1, 2]. Major clinical practice guidelines, including those from the National Comprehensive Cancer Network, highlight their importance in lymphoid malignancies, collectively positioning standardized genomic testing as a key component of diagnosis, therapeutic decision-making, and prognostic assessment in current lymphoma care [3, 4].

Despite this progress, implementing next-generation sequencing (NGS)-based testing in routine diagnostic laboratories remains challenging. Comprehensive genomic panels typically require substantial bioinformatic infrastructure, specialized personnel, and extended turnaround times that may not align with time-sensitive clinical decision-making. Laboratories must also accommodate diverse sample types, including formalin-fixed paraffin-embedded (FFPE) tissues, bone marrow aspirates, peripheral blood, and body fluids, which differ in DNA quality and can impact assay performance [5, 6]. Consequently, the demand for robust, rapid, and clinically practical NGS assays specifically optimized for routine lymphoma diagnostics is growing [7].

In this issue of *Annals of Laboratory Medicine*, Krigstein *et al*. [8] report the clinical validation of the Ion AmpliSeq Liverpool Lymphoid Network Panel (IALLNP; Thermo Fisher Scientific, Waltham, MA, USA) on the Ion Torrent Genexus Integrated Sequencer (Thermo Fisher Scientific). The IALLNP is a commercially available amplicon-based DNA sequencing assay that targets 60 clinically relevant genes, including the complete coding regions of 17 genes and selected exonic hotspots in 43 genes recurrently mutated in lymphoid malignancies. The panel detects single-nucleotide variants (SNVs) and small insertions/deletions (indels).

For analytical validation, the authors used 54 clinical DNA samples together with a commercial reference standard. The clinical cohort comprised FFPE lymph node tissues (N=22), bone marrow aspirates (N=22), and peripheral blood samples (N=10), covering a broad spectrum of lymphoid malignancies, including chronic lymphocytic leukemia, mantle cell lymphoma, diffuse large B-cell lymphoma, marginal zone lymphoma, primary mediastinal B-cell lymphoma, Waldenstrom's macroglobulinemia, and T-cell lymphomas. All clinical samples were previously tested by a hybridization capture–based NGS assay at an external accredited laboratory, enabling direct assessment of concordance. Notably, differences in the distribution of lymphoma subtypes and in the genetic landscape according to ethnicity should also be considered [9].

After optimization for poorly performing amplicons and recur-

rent artifacts, the IALLNP showed good overall performance in terms of depth of coverage, on-target reads, and coverage uniformity. Across validation runs, the mean depth was 2,494×, with mean uniformity of 94%. For the retained 1,319 amplicons, an average of 99.27% of targeted bases were covered at ≥100× and 96.57% at ≥350×. Non-template controls showed minimal background signal, further supporting the analytical robustness of the workflow. FFPE samples demonstrated slightly shorter mean read length, and marginally lower uniformity than bone marrow/peripheral blood samples but comparable mean depth, indicating that the assay is generally robust across sample types used in routine practice.

Using an externally validated NGS assay as reference, the authors identified 168 assessable variants, of which the IALLNP detected 153 (91%). All 20 assessable variants in the commercial SeraSeq Lymphoma DNA Mutation Mix (SeraCare, Milford, MA, USA) were detected. Detection rates were 100% (135 of 135) for variants with a variant allele frequency (VAF) ≥5%, 73% (16 of 22) for variants with VAF 3%–4.9%, and 8% (2 of 11) for variants with VAF<3%. VAFs showed a strong correlation between platforms (R^2=0.9347). Overall, the panel achieved 100% sensitivity for SNVs and indels at a validated lower limit of detection of 5% VAF, with 100% specificity in variant-negative samples and a mean of 0.4 for easily recognizable false-positive variants per sample that could be excluded upon review of raw data.

Importantly, the panel demonstrated 92.8% reproducibility; all nonreproducible variants occurred below the 5% VAF analytical threshold, consistent with the defined limit of detection and emphasizing the need for caution in interpreting very low–VAF calls.

A distinct strength of the evaluated workflow is its rapid turnaround time. The Ion Torrent Genexus Integrated Sequencer performs automated barcoded library preparation, templating, and sequencing, with integrated primary data analysis, and can accommodate up to 15 samples plus a no-template control per run on the GX5 chip. This configuration delivered the genetic results for lymphoid neoplasms within a clinically meaningful timeframe of approximately 2 days from DNA extraction, which is particularly valuable in settings where timely molecular data can inform initial treatment choices or enrollment in targeted-therapy trials.

Several important limitations must be acknowledged. As an amplicon-based DNA assay without unique molecular identifiers, the IALLNP is optimized for the detection of SNVs and small indels but does not assess copy number changes, structural rearrangements, or aneuploidies, all of which remain critical components of the diagnostic work-up for many lymphoid neoplasms. In addition, their initial sequencing runs revealed consistently underperforming amplicons, often in GC-rich or repetitive regions, which required exclusion from the target region definition after confirming the absence of recurrent clinically significant variants at those loci. The authors also emphasize that careful bioinformatic optimization, including tailored filter settings, exclusion of common polymorphisms, and comprehensive variant curation, is essential to minimize false-negative and false-positive calls, particularly for low-VAF variants.

Manual review and expert interpretation remain indispensable steps in the overall workflow. Candidate variants were visually inspected in Integrative Genomics Viewer (IGV; Broad Institute, Cambridge, MA, USA) and annotated using established somatic and population databases, with clinical significance assigned according to a modified version of the College of American Pathologists/Association for Molecular Pathology consensus guidelines [10]. This iterative process highlights that even within an automated "sample-to-report" platform, high-quality molecular diagnostics for lymphoid neoplasms require experienced molecular pathologists and robust variant interpretation frameworks.

Finally, the IALLNP must be viewed within an evolving genomic landscape. Although the panel covers many of the key genes implicated in lymphoid neoplasms, including entities where recurrent mutations (e.g., *MYD88*, *SF3B1*, *RHOA*, *EZH2*, *TP53*, *BTK*, *PLCG2*) can aid in diagnosis, risk stratification, and prediction of response or resistance, new biomarkers and therapeutic targets continue to emerge. Maintaining clinical relevance will therefore require periodic updates to panel content and ongoing alignment with WHO and ICC classifications and with rapidly changing treatment paradigms, including covalent and noncovalent BTK inhibitors, BCL2 inhibitors, and epigenetic therapies [11, 12].

Despite these limitations, the study by Krigstein *et al*. demonstrates that a targeted, lymphoma-focused NGS panel can be successfully implemented as part of routine diagnostic workflow using a fully integrated sequencing platform. By combining streamlined automation with clinically focused gene coverage and well-defined analytical performance, the IALLNP offers a practical balance between depth of genomic information, turnaround time, and operational feasibility for routine hematopathology practice. As genomic profiling continues to reshape the diagnostic paradigm for lymphoid neoplasms, the integration of rapid targeted NGS panels, such as the IALLNP, into routine workflows is likely to become an increasingly important comple-

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ment to morphology, immunophenotyping, and cytogenetics in precision lymphoma care.

AUTHOR CONTRIBUTIONS

Shin S and Lee ST wrote and revised the manuscript. Lee ST reviewed and approved the final manauscript.

CONFLICTS OF INTEREST

None declared.

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