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Gene expression profiling for cell-of-origin determination in diffuse large B-cell lymphoma

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Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, comprising approximately 25-30% of adult non-Hodgkin lymphomas in western countries and consists of a clinically heterogeneous group that exhibits similarities in morphology and immunophenotype. However, it was found that Gene Expression Profiling (GEP) could further classify DLBCLs into distinct molecular subgroups based on Cell-of-Origin (COO), including the Germinal Center B-cell type (GCB), Activated B-Cell type (ABC), or Unclassified (UNC) type, and that these subtypes had important prognostic significance, such that patients with ABC type DLBCL exhibited a significantly worse outcome when treated with R-CHOP (Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) chemotherapy regimens. However, this classification method required the use of fresh or fresh-frozen tissue for GEP COO assignment using the Affymetrix microarray platform (Santa Clara, CA) and was not practical for everyday clinical use. This led to the development of more practical and less expensive immunohistochemistry-based methods for assignment of COO, with the Hans algorithm being the most popular because it required only a small number of immunohistochemical stains (CD10, BCL6 and MUM1) to classify cases as GCB or non-GCB DLBCL subtypes and could also utilize readily available Formalin-Fixed Paraffin-Embedded (FFPE) tissue. However, immunohistochemical assignment of DLBCL COO suffers from poor reproducibility and agreement with the gold standard GEP assay. In order to make molecular COO assignment of DLBCLs more practical, accurate and reproducible, a GEP assay was developed for COO assignment using FFPE tissue by the Lymphoma/Leukemia Molecular Profiling Project (LLMPP), known as the Lymph2Cx assay. This assay uses a 20-gene panel and includes eight genes overexpressed in ABC, seven genes overexpressed in GCB and five housekeeping genes. This 20-gene panel demonstrated more than 95% concordance of COO assignment when compared with the original microarray-based assay developed using frozen tissue samples, making it a viable alternative for testing in a conventional clinical molecular diagnostic laboratory setting. We developed the first clinical GEP assay and validated to perform COO assignment of DLBCL in a College of American Pathologists/Clinical Laboratory Improvement Amendments (CAP/CLIA)-certified molecular diagnostics laboratory in the United States and have demonstrated how this assay can be incorporated into the routine workup of DLBCL cases through analysis of over 100 DLBCL cases using the Lymph2Cx clinical assay.

Biography

Ryan S Robetorye has received his MD and PhD degrees from Baylor College of Medicine in Houston, Texas. He is board certified in Clinical Pathology, Hematology and Molecular Genetic Pathology and currently works as a Consultant at the Mayo Clinic in Phoenix, Arizona. He currently serves as the Medical Director of the Clinical Laboratories at the Mayo Clinic. His research interests primarily involve hematological malignancies and molecular diagnostics involving gene expression profiling and next-generation sequencing.

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