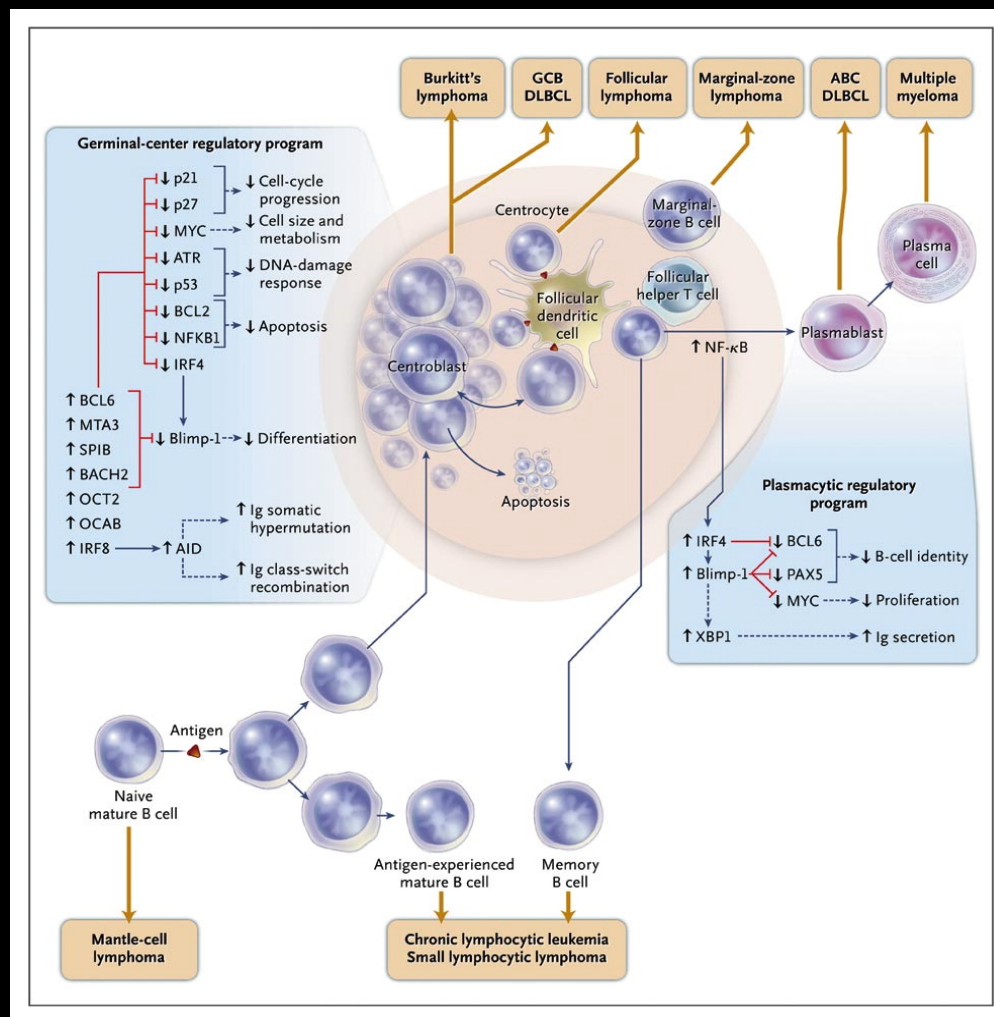


B-Cell Differentiation and Lymphomagenesis



Lenz G, Staudt LM. *N Engl J Med* 2010;362:1417-1429.



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Figure 1. B-Cell Differentiation and Lymphomagenesis. Malignant lymphomas can arise at multiple stages of normal B-cell development. After the stimulation of a mature naive B cell with a T-cell–dependent antigen, the germinal-center reaction is initiated. The germinal-center B cell represents a discrete, quasi-stable differentiation stage that is characterized by a unique regulatory network and the action of activation-induced cytidine deaminase (AID), which induces both immunoglobulin (Ig) somatic hypermutation and heavy-chain class switching. Several transcription factors are required to establish and maintain the identity and function of the germinal-center B cell, including BCL6, MTA3, SPIB, BACH2, OCT2, OCAB, and IRF8. Red lines indicate that a regulatory factor inhibits the indicated gene or cellular function, and blue lines indicate positive regulation. In concert, these factors block plasmacytic differentiation by repressing Blimp-1. They also promote cell-cycle progression without cell growth while blocking the DNA damage response evoked by AID-dependent mutations and DNA breaks. Within the germinal center, the rapidly proliferating centroblasts are prone to cell death. Periodically, centroblasts travel to a subcompartment of the germinal center that is rich in follicular dendritic cells and follicular helper T cells, where they become centrocytes. Centrocytes may be rescued from cell death as a result of stimulation by antigen on follicular dendritic cells and CD40 ligand on T cells and may then revert to the centroblast state and resume proliferation. IRF4 initiates plasmacytic differentiation by establishing a characteristic regulatory network, which extinguishes the mature B-cell program while promoting terminal differentiation and immunoglobulin secretion. The putative origins of various non-Hodgkin's lymphomas — including the germinal-center B-cell–like (GCB) and activated B-cell–like (ABC) subtypes of diffuse large-B-cell lymphoma (DLBCL) — are indicated. Lymphomas that are derived from germinal-center B cells have recurrent genetic abnormalities that circumvent the normal genetic program in order to block plasmacytic differentiation, promote cell growth, and evade apoptosis. NF- κ B denotes nuclear factor- κ B.

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

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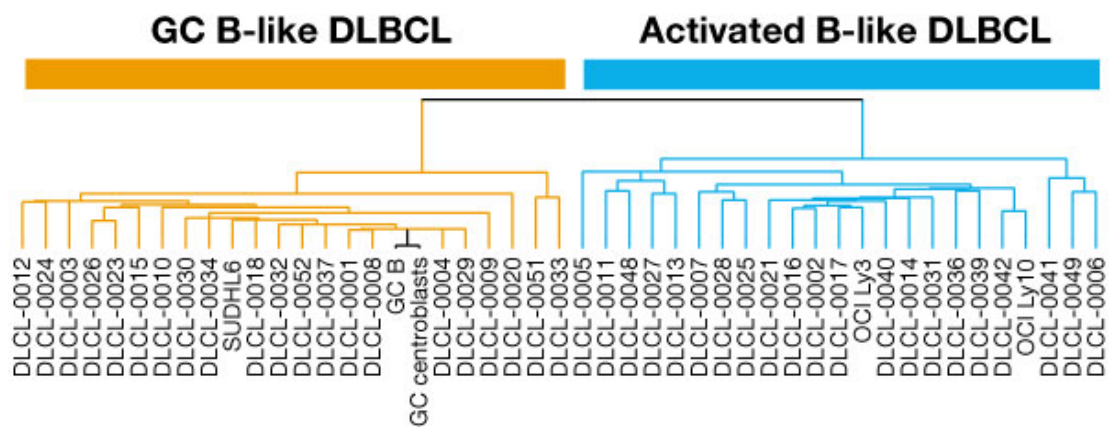
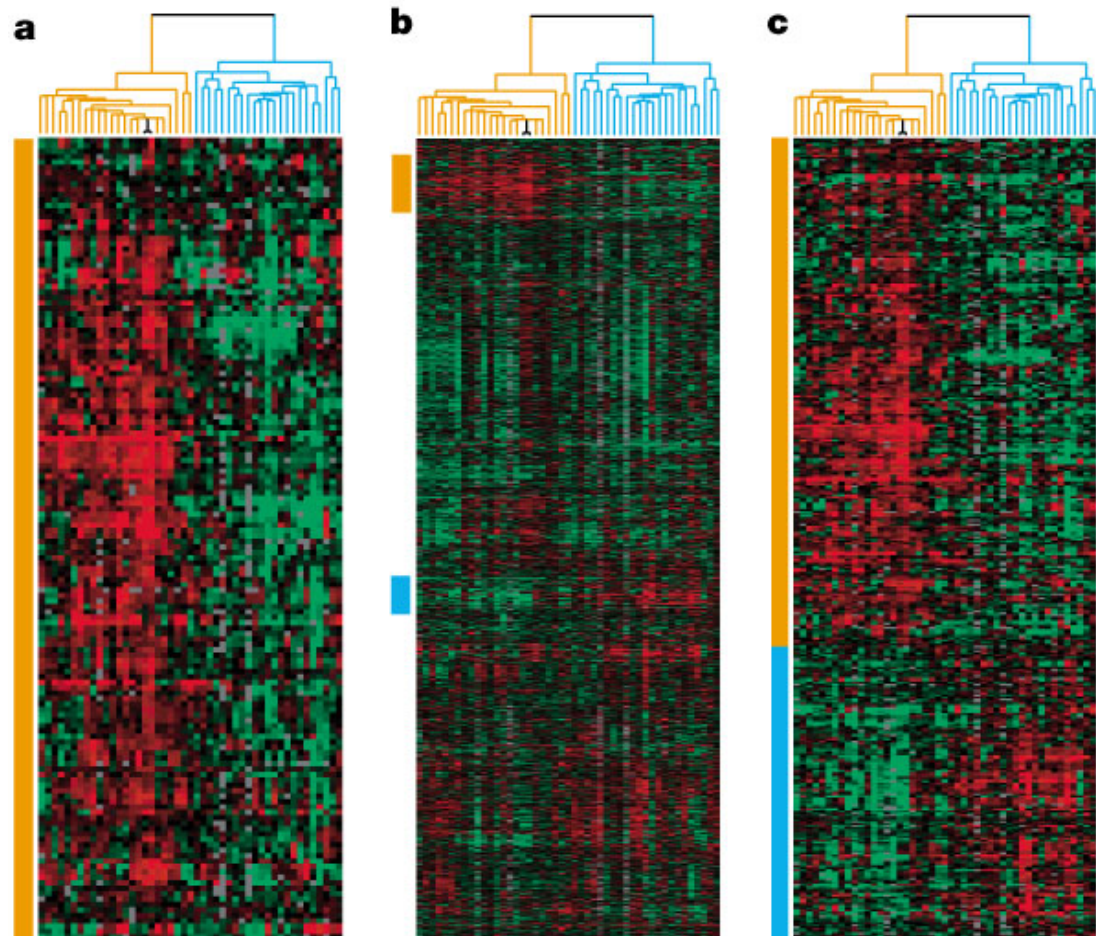
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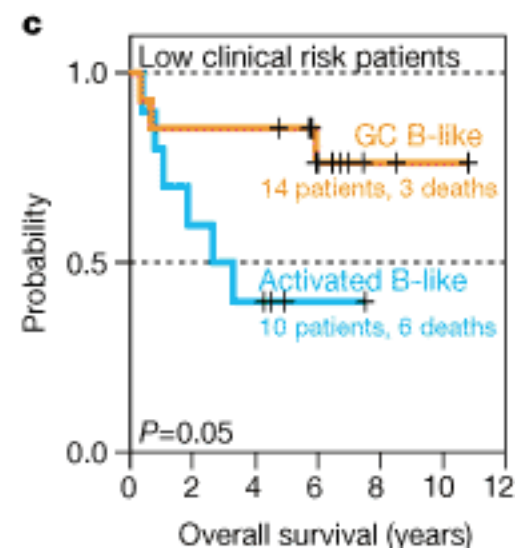
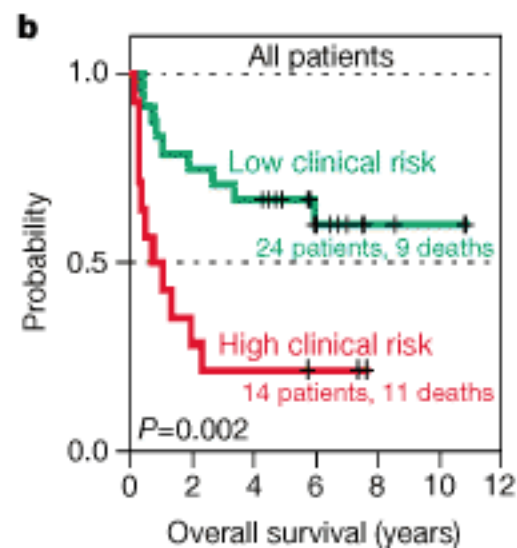
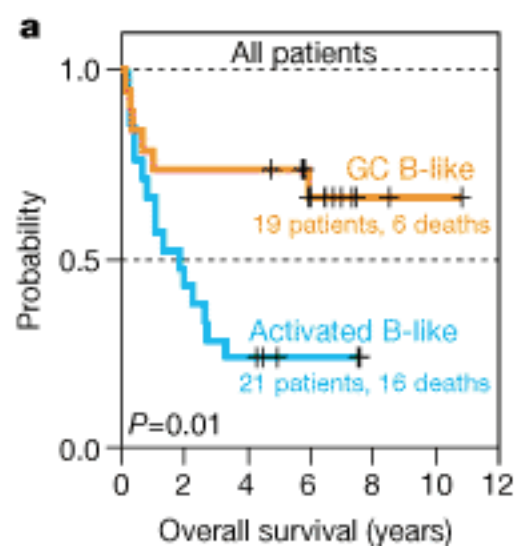
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Diffuse large B-cell lymphoma (DLBCL), the most common subtype of non-Hodgkin's lymphoma, is clinically heterogeneous: 40% of patients respond well to current therapy and have prolonged survival, whereas the remainder succumb to the disease. We proposed that this variability in natural history reflects unrecognized molecular heterogeneity in the tumours. Using DNA microarrays, we have conducted a systematic characterization of gene expression in B-cell malignancies. Here we show that there is diversity in gene expression among the tumours of DLBCL patients, apparently reflecting the variation in tumour proliferation rate, host response and differentiation state of the tumour. We identified two molecularly distinct forms of DLBCL which had gene expression patterns indicative of different stages of B-cell differentiation. One type expressed genes characteristic of germinal centre B cells ('germinal centre B-like DLBCL'); the second type expressed genes normally induced during *in vitro* activation of peripheral blood B cells ('activated B-like DLBCL'). Patients with germinal centre B-like DLBCL had a significantly better overall survival than those with activated B-like DLBCL. The molecular classification of tumours on the basis of gene expression can thus identify previously undetected and clinically significant subtypes of cancer.





Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray

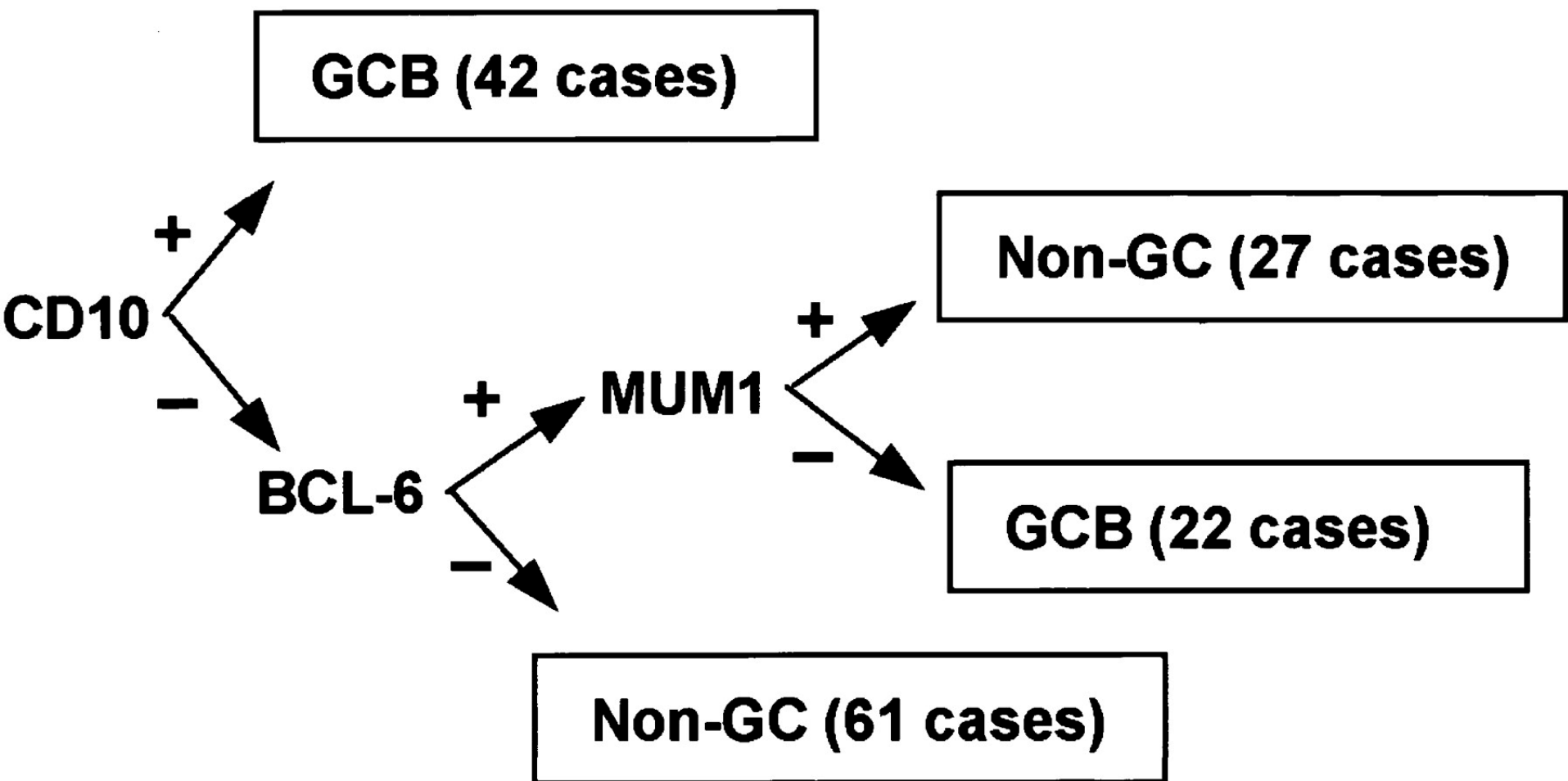
Christine P. Hans, Dennis D. Weisenburger, Timothy C. Greiner, Randy D. Gascoyne, Jan Delabie, German Ott, H. Konrad Müller-Hermelink, Elias Campo, Rita M. Braziel, Elaine S. Jaffe, Zenggang Pan, Pedro Farinha, Lynette M. Smith, Brunangelo Falini, Alison H. Banham, Andreas Rosenwald, Louis M. Staudt, Joseph M. Connors, James O. Armitage, and Wing C. Chan

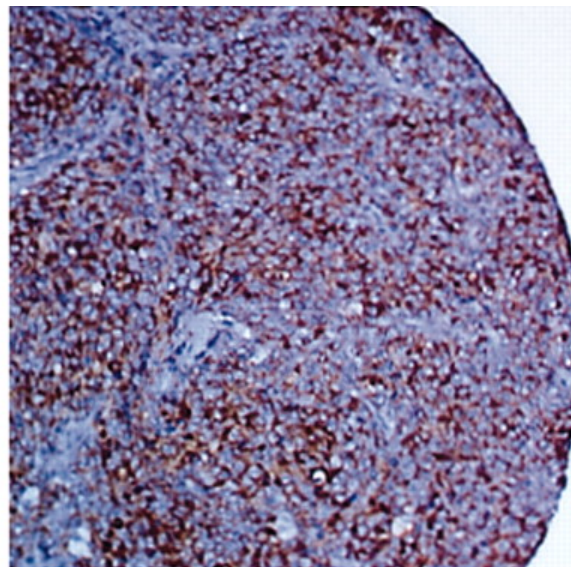
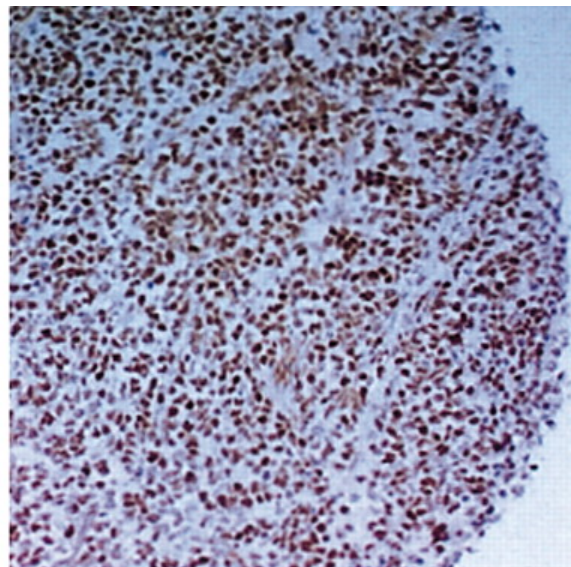
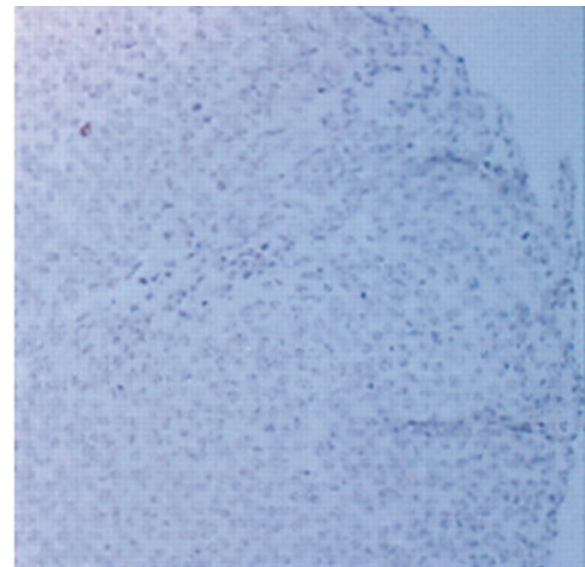
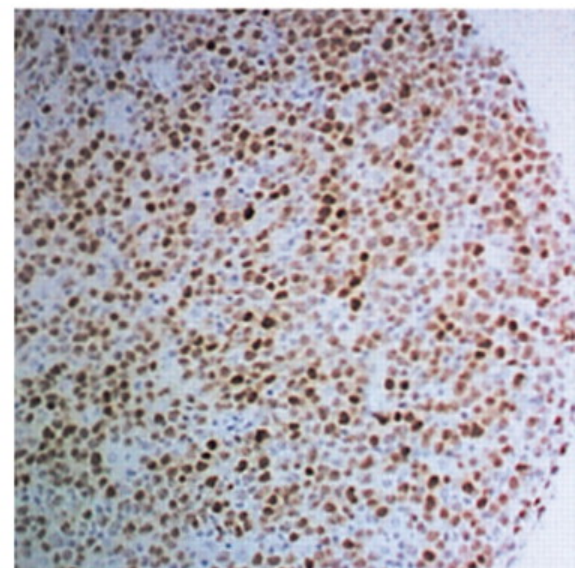
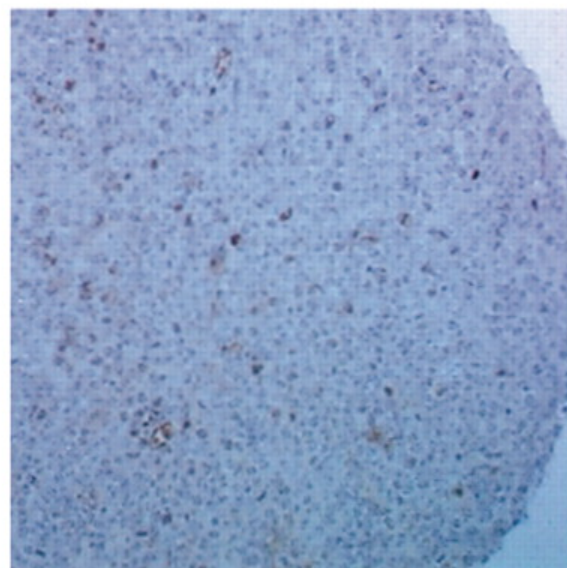
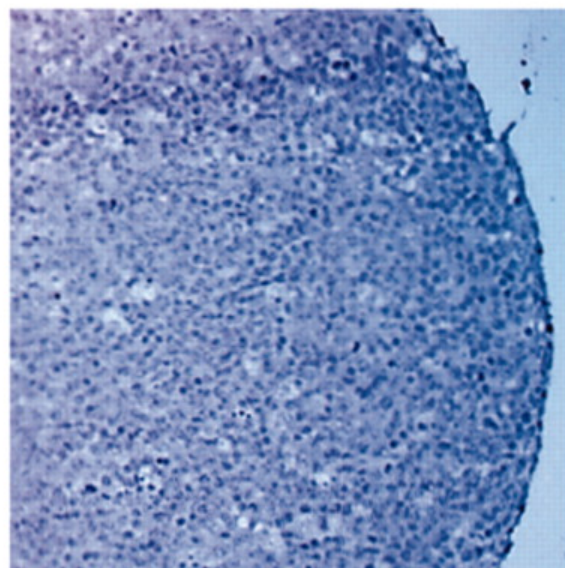
Diffuse large B-cell lymphoma (DLBCL) can be divided into prognostically important subgroups with germinal center B-cell-like (GCB), activated B-cell-like (ABC), and type 3 gene expression profiles using a cDNA microarray. Tissue microarray (TMA) blocks were created from 152 cases of DLBCL, 142 of which had been successfully evaluated by cDNA microarray (75 GCB, 41 ABC, and 26 type 3). Sections were stained with antibodies to CD10, bcl-6, MUM1, FOXP1, cyclin D2,

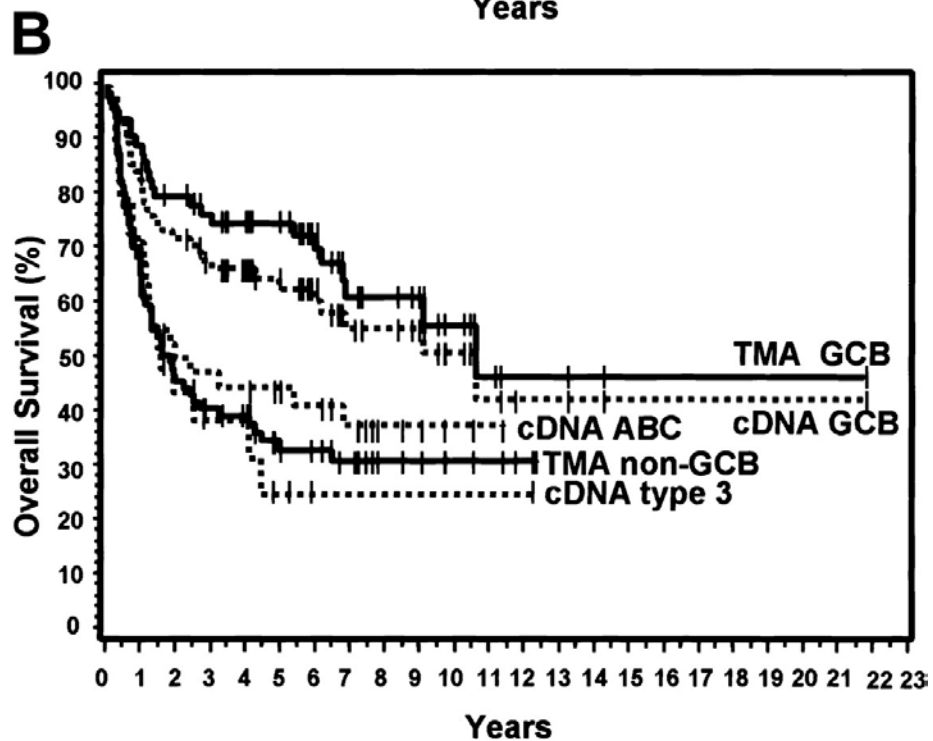
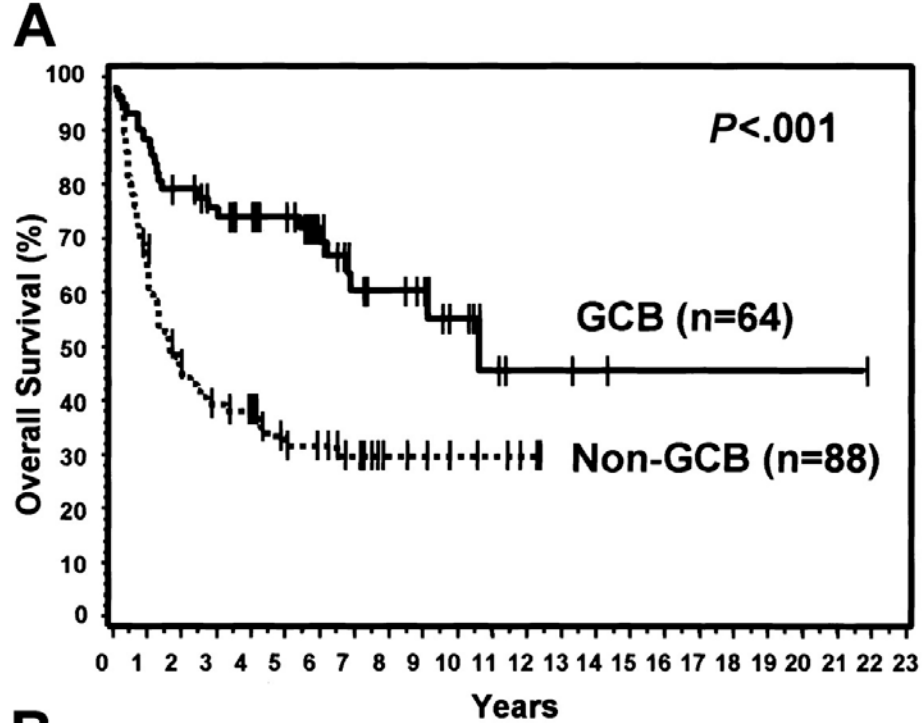
and bcl-2. Expression of bcl-6 ($P < .001$) or CD10 ($P = .019$) was associated with better overall survival (OS), whereas expression of MUM1 ($P = .009$) or cyclin D2 ($P < .001$) was associated with worse OS. Cases were subclassified using CD10, bcl-6, and MUM1 expression, and 64 cases (42%) were considered GCB and 88 cases (58%) non-GCB. The 5-year OS for the GCB group was 76% compared with only 34% for the non-GCB group ($P < .001$), which is similar to that reported using the

cDNA microarray. Bcl-2 and cyclin D2 were adverse predictors in the non-GCB group. In multivariate analysis, a high International Prognostic Index score (3-5) and the non-GCB phenotype were independent adverse predictors ($P < .0001$). In summary, immunostains can be used to determine the GCB and non-GCB subtypes of DLBCL and predict survival similar to the cDNA microarray. (Blood. 2004;103:275-282)

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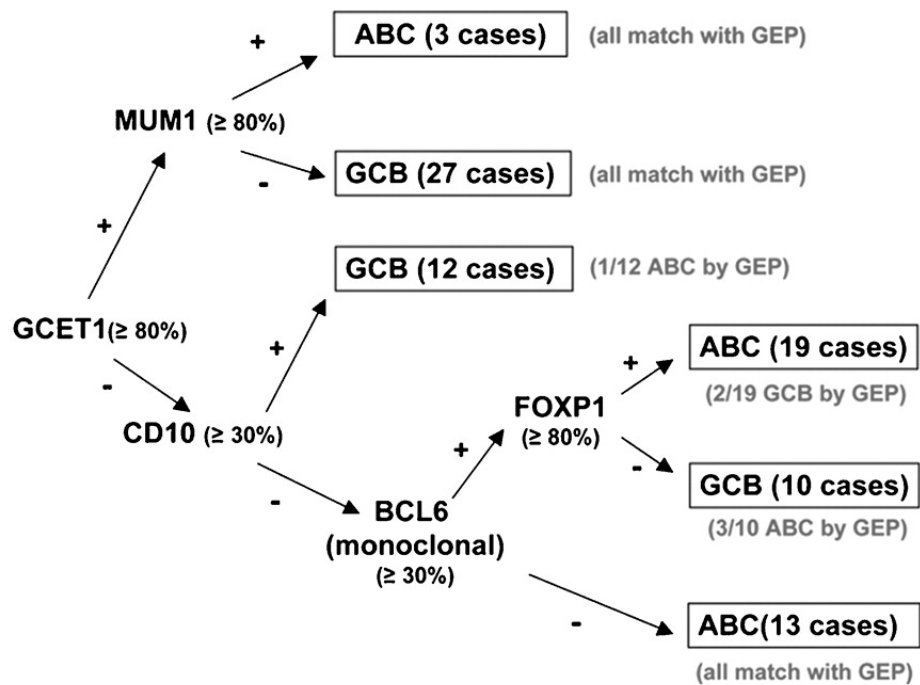


A**CD10****BCL-6****MUM1****B**



A

New Algorithm



B

Hans' Algorithm

