MatBA® DLBCL

INFORM PREDICT DECIDE

Mature B-Cell Neoplasm Array

MatBA®-DLBCL Array-CGH Assay

for the clinical management of diffuse large B-cell lymphoma

INFORM

MatBA®-DLBCL assesses **multiple prognostic genomic biomarkers**.

PREDICT

Based on individual biomarkers and genomic complexity, the clinician can predict whether the patient has an overall **adverse outcome**.

DECIDE

Together with other clinical and laboratory findings, MatBA®-DLBCL can assist in devising the **best treatment plan for an individual patient**.

CLIA and New York State Approved

For more information, please visit www.cgimatba.com

CANCER GENETICS

Empowering Personalized Cancer Treatment

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Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL is the most common form of non-Hodgkin lymphoma (NHL) accounting for 40% of all NHL cases worldwide and about 90% of aggressive B-cell lymphomas in the western world.

DLBCLs display marked clinical, pathologic, and genetic heterogeneity and if left untreated, take an aggressive and fatal clinical course. About 40% of patients are cured by current frontline treatment comprising immunochemotherapy and 60% succumb to their disease, mostly within the first 2-3 years following treatment. Given the median age of diagnosis of DLBCL at 64 years, the comorbid conditions often observed in older patients, and the need to identify those patients most likely not to be cured, risk-stratification is highly desirable. Currently, risk stratification of DLBCL patients is based on clinical features according to the International Prognostic Index (IPI) score which is used as part of the current National Comprehensive Cancer Network (NCCN) treatment protocol for DLBCL. The inclusion of additional biomarkers in risk stratification could enhance the potential to identify those patients most likely to have refractory disease or have an early relapse, in order to individualize treatment strategies countenancing efficacy and tolerability in the patient.

Adverse Risk Factors for IPI Scoring
Age > 60 years
LDH level above normal
High ECOG Performance Status
Stage III or IV
More than 1 extranodal site

Molecular profiling of DLBCL at both the gene expression and genomic levels has uncovered molecular biomarkers of outcome. Cell-of-origin subtypes based on gene expression signatures display differential outcomes: patients with DLBCL of the GCB subtype have a more favorable outcome compared to DLBCL of the ABC or non-GCB subtypes. At the genomic level, DLBCLs with rearrangement at the *MYC* (8q24) locus, have an overall poor clinical course and if identified early, could allow the selection of a treatment strategy suitable for a high risk patient. DLBCLs also exhibit genomic copy number alterations (CNAs), evidenced as gain or loss of individual genomic loci. A variety of studies have revealed the prognostic significance of select CNAs, such that DLBCL patients with these aberrations exhibit an overall unfavorable outcome. Additionally, an overall adverse outcome is observed in DLBCLs exhibiting a more complex pattern of genomic gains and losses.

Considering the evolving therapeutic landscape in hematologic cancers, inclusion of such molecular biomarkers in risk stratification of DLBCL will favorably impact informed treatment decisions in this disease.

The MatBA®-DLBCL assay uses array-based comparative genomic hybridization technology (array-CGH) to assess both individual CNA and genomic complexity as indicators of a poor outcome following immunochemotherapy in DLBCL patients.

NCCN Guidelines: Current DLBCL Treatment Recommendations

Stage I, II	Nonbulky (<10 cm)	Adverse risk factors present (IPI)	RCHOP x 3 cycles + Radiation Therapy or RCHOP x 6 cycles ± Radiaton Therapy
		Adverse risk factors not present (IPI)	
	Bulky (≥10 cm)		RCHOP x 6 cycles ± Radiation Therapy
Stage III, IV			RCHOP x 6 cycles ± Radiation Therapy or Clinical Trial

Note: For full testing guidance, see the NCCN Guidelines for DLBCL.

The Process of Array-CGH

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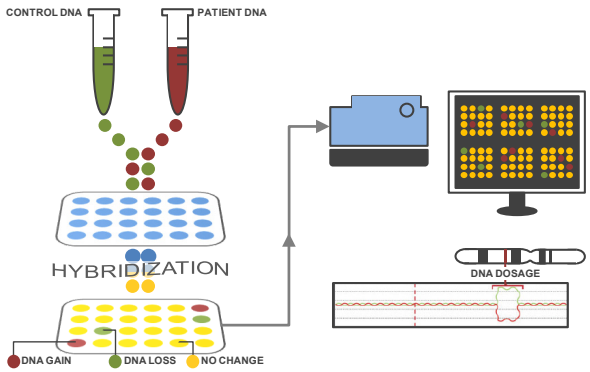
1. Patient and control DNA labeled with fluorescent dyes are applied to the microarray.
2. Patient and control DNA are hybridized to the microarray.
3. The fluorescent signals are measured by the microarray scanner.
4. Next, the data is analyzed by computer software which then generates a plot.



MatBA® DLBCL
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Mature B-Cell Neoplasm Array

MatBA®-DLBCL Array-CGH Assay

In a Single Test, MatBA®-DLBCL Array-CGH Assesses Individual Prognostic Biomarkers and Genomic Complexity

- MatBA®-DLBCL has prognostic value
- MatBA®-DLBCL assists in patient stratification for risk-adapted therapy when performed at diagnosis
- MatBA®-DLBCL assesses the presence of individual prognostic markers as well as genome complexity as measures of overall survival following front-line immunochemotherapy

Individual Prognostic Markers

The presence of one or more of the below genomic aberrations is associated with an overall adverse outcome.

• Loss of 6q21 (*PRDM1*)	• Loss of 8p23.3-p21.3	• Gain of 8q24 (*MYC*)
• Loss of 6q23.3-q24 (*TNFAIP3*)	• Gain of 3q22-q27	• Gain of 18q21 (*BCL2*)
• Loss of 17p13 (*TP53*)	• Loss of 9p21 (*CDKN2A*)	

Patient category that may benefit from a more rigorous treatment regimen

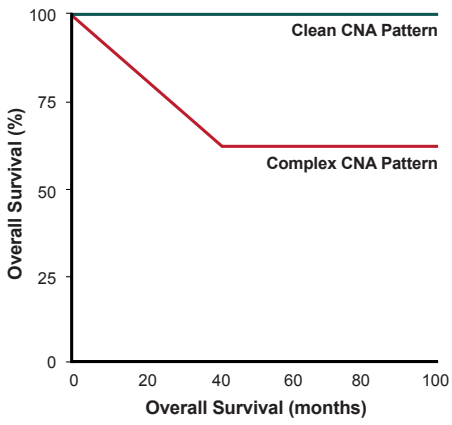
Genomic Complexity

A recent study identified a set of copy number alterations (CNAs) in newly diagnosed DLBCL specimens found to decrease TP53 activity and disrupt cell cycle regulation. DLBCL specimens exhibiting these CNAs were termed “complex” while those lacking them were termed “clean.” The “complex” CNA pattern was found to be highly predictive for outcome in R-CHOP treated patients. Patients with a “complex” CNA pattern exhibited a poor overall survival compared to patients with a “clean” CNA pattern.

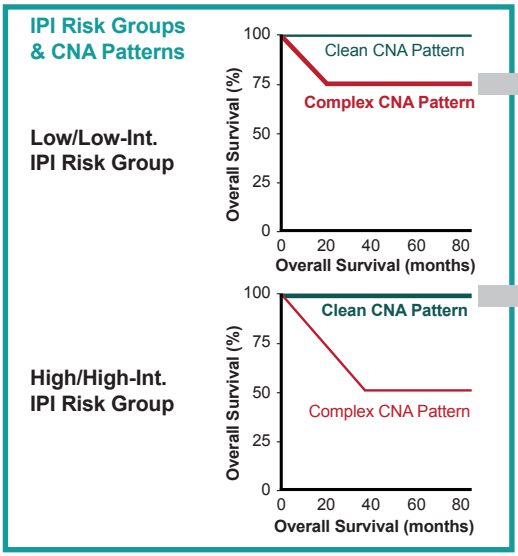
The CNA pattern was found to also significantly increase prognostic accuracy within different clinical IPI risk groups as well. Patients exhibiting a “complex” CNA pattern had significantly shorter overall survival compared to their “clean” counterparts in both low/low-intermediate and high-intermediate/high risk groups.

An assessment of genomic complexity can further stratify patients within IPI risk groups.

Copy Number Alteration (CNA) Patterns



IPI Risk Groups & CNA Patterns



Adapted from Monti et al., 2012

Patient category that may benefit from a more rigorous treatment regimen

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Impact on treatment decision

Assay Specifications

Sensitivity

Limit of detection is 60-70 cells in 100 cells for formalin-fixed paraffin-embedded (FFPE) specimens and 50-60 cells in 100 for fresh-frozen specimens.

Specimen Requirements

FFPE block: containing ≥ 70% tumor. Minimum size: 2 mm x 2 mm tumor area, shipped at room temperature.
Fresh-Frozen tissue: 0.2 cm^3 min. (in OCT is acceptable) containing ≥ 50% tumor. Stored at -80°C /-20°C, shipped on dry ice.
FFPE block or fresh-frozen specimen: incisional or excisional biopsy.

CPT Code: 81479

Turnaround Time: 10-14 days

MatBA® - DLBCL Array-CGH Report

Results:

Genomic Aberration	*Result*	*CDKN2A-TP53-RB-E2F Axis Aberrations*[4]	*Result*
Gain of 3q22-q27	NEGATIVE	Loss of 17p13 (*TP53*)	**POSITIVE**
Loss of 6q21 (*PRDM1*)	NEGATIVE	Loss of 9p21 (*CDKN2A*)	NEGATIVE
Loss of 6q23.3-q24 (*TNFAIP3*)	**POSITIVE**	Gain of 1q21-q31	NEGATIVE
Loss of 8p23.3-p21.3	**POSITIVE**	Gain of 6p21.1	NEGATIVE
Gain of 8q24 (*MYC*)	**POSITIVE**	Gain of 7p22-q31	NEGATIVE
Gain of 18q21 (*BCL2*)	**POSITIVE**	Gain of 12q13-q15	NEGATIVE
		Loss of 13q14	NEGATIVE
		Loss of chr16	NEGATIVE
		Gain of 19q13.33-q13.43	NEGATIVE

Interpretation: ***Positive for the gain of 8q24 (MYC) and 18q21 (BCL2) and loss of 6q23.3-q24 (TNFAIP3), 8p23.3-p21.3 and 17p13 (TP53).***

Description:

The gain and loss of genomic regions in Diffuse Large B-Cell Lymphoma (DLBCL) are considered to have prognostic value. Gains of 3q, 8q (*MYC*) and 18q (*BCL2*) and loss of 9p (*CDKN2A*), 17p (*TP53*) and 6q (*PRDM1/BLIMP1* and/or *TNFAIP3/A20*) have been associated with shorter overall survival with current therapy (1-3). Genomic imbalance of the CDKN2A-TP53-RB-E2F axis are reflective of a complex pattern of copy number alterations associated with an increased proliferation index and adverse outcome (4).

This assay utilizes microarray based comparative genomic hybridization (array CGH) to simultaneously detect the gain and loss of multiple loci in specimen DNA. Quantitative PCR is used to confirm the detected genomic gains and losses. The sensitivity of the assay is 60-70% for formalin-fixed paraffin-embedded specimens and 50-60% for fresh frozen specimens. Aberrations may not be detected in samples in which the tumor percentage is less than the assay sensitivity. The test results should not be used solely for prognostication and should be interpreted in the context of other clinical and laboratory findings.

References:

1. Lenz G, et al, Mol subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A 2008, 105(36):13520-13525.
2. Yoon SO, et al. MYC translocation and an increased copy number predict poor prognosis in adult diffuse large B-cell lymphoma (DLBCL), especially in germinal centre-like B cell (GCB) type. Histopathology 2008:53(2):205-17.
3. Dierlamm J, et al., Gain of chromosome region 18q21 including the MALT1 gene is associated with the activated B-cell-like gene expression subtype and increased BCL2 gene dosage and protein expression in diffuse large B-cell lymphoma. Haematologica. 2008 May; 93(5):688-96.
4. Monti, S., et al. Integrative analysis reveals an outcome-associated and targetable pattern of p53 and cell cycle deregulation in diffuse large B cell lymphoma. Cancer Cell: 2012, 22(3):359-72.

Licensure

CAP (Laboratory #: 7191582, AU-ID: 1434060), CLIA (Certificate #: 31D1038733), New Jersey (CLIS ID #: 0002299), New York State (PFI: 8192), Pennsylvania (031978), Florida (800018142), Maryland (1395).