CANCER GENETICS®

Empowering Personalized Cancer Treatment

CLL COMPLETE

CLL Complete™

Approximately 16,000 new cases of chronic lymphocytic leukemia (CLL) are diagnosed annually in the U.S. Accurate prognostication for treatment options is highly desirable in CLL considering that it occurs almost exclusively in adults and that patients display great clinical heterogeneity in the course of their disease. Some patients have aggressive disease requiring careful active monitoring or treatment at diagnosis. Others exhibit an indolent course involving different clinical management. Risk stratification based on clinical stage, fitness and comorbidities, and molecular prognostic markers is highly recommended at diagnosis. Importantly, risk stratification throughout the course of the disease is recommended depending on the age of CLL patients and the underlying biology of the disease.

List of CLL Complete™ Tests

Physicians can order tests individually or allow CGI pathologists and directors to determine a panel evaluation as determined necessary.

Morphology & IHC

Morphology
Morphological and histologic subtype assessments provide diagnostic information for the disease.

B-Cell Lymphoma Panel - IHC
This panel provides diagnostic information on the immunophenotype of the disease. The antibodies included in this panel are CD3, CD5, CD10, CD20, PAX5, CD21, CD23, CD43, CD79a, Bcl-2, Bcl-6, CyclinD1, and Ki-67.

Flow Cytometry

CD38
CD38 has been identified as an independent prognostic marker and high expression is associated with an unfavorable clinical course.

ZAP-70
ZAP-70 is an independent prognostic marker that is also used as a surrogate marker for IGHV mutation analysis. High levels of the ZAP-70 protein correlate with aggressive disease. In addition to ZAP-70, this panel includes CD3, CD5, CD19, and CD45.

MRD-CLL
MRD-CLL by flow cytometry is used to monitor patients who are undergoing therapy for CLL and provides a quantitative measurement of MRD status. A MRD-CLL negative status is associated with improved overall survival and progression-free survival. The sensitivity of the flow assay is 10^{-4}.

Molecular Diagnostics

Focus::CLL™ NGS Panel [CLIA approved]
The Focus::CLL™ NGS panel assists in the prognosis of CLL patients. Multiplexed sequencing by synthesis is performed using the MiSeq System (Illumina). This panel includes selected exons of the *TP53*, *NOTCH1*, *SF3B1*, *BIRC3*, *ATM*, *MYD88*, and *CARD11* genes.

MatBA®-CLL/SLL Array-CGH [CLIA and New York State approved]
Clonal genomic alterations with diagnostic and prognostic significance are assayed by array-comparative genomic hybridization (array-CGH) permitting the simultaneous detection of gain and loss at multiple loci. Loci being assessed by MatBA®-CLL/SLL are 1p, 2p, 3q, 4p, 5p, 6q, 7p, 7q, 8p, 8q, 11q (*ATM*), 12q, 13 (*MIR15A/16-1*), 17p (*TP53*), 17q, 18p, 18q, and 19p.

IGHV Mutation Analysis
Detection of hyper-mutation in the *IGHV* gene serves as an independent prognostic marker. Patients with the hyper-mutated *IGHV* gene exhibit a better overall survival than those with un-mutated *IGHV*. Utilization of *IGHV3-21* regardless of *IGHV* mutation status is associated with an unfavorable outcome.

TP53 Mutation Analysis
The presence of a *TP53* mutation is associated with shorter survival and resistance to chemotherapy.

NOTCH1 Mutation Analysis
Mutational *NOTCH1* activation in CLL diagnosis is an independent predictor of poor survival and a shorter time to progression.

SF3B1 Mutation Analysis
SF3B1 mutations are independent predictors that occur in 10-15% of CLL patients and are indicative of shorter time to treatment, and a poorer overall survival.

FISH

FDA-Approved FISH Panel
The FISH analysis provides high sensitivity information about key genomic alternations and prognostic markers, such as the loss of 17p (*TP53*), 11q (*ATM*), 13q, and 6q, along with the gain of chromosome 12. The translocation t(11;14) is also evaluated to rule out Mantle Cell Lymphoma.

Karyotyping
Karyotyping enables genome-wide detection of aberrations at low resolution that have a diagnostic and prognostic significance.

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CANCER GENETICS®

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CLL COMPLETE

Diagnostic Work Up for CLL Complete™

New Diagnosis or Disease Monitoring

RISK STRATIFICATION

IHC & Flow Cytometry

Morphology; Immunophenotyping; CD38; ZAP-70; MRD-CLL

Cytogenetics

CLL FISH Panel; Karyotype

Molecular Diagnostics

IGHV Mutation Analysis

MatBA®-CLL/SLL Array-CGH

Focus::CLL™ NGS Panel:
NOTCH1, SF3B1, TP53, BIRC3, ATM, MYD88, & CARD11

Other Individual Mutation Analyses:
NOTCH1, SF3B1, & TP53

Relapse or Prior to Treatment

RISK STRATIFICATION THERAPY GUIDANCE

Cytogenetics

CLL FISH Panel

Karyotype

Molecular Diagnostics

MatBA®-CLL/SLL Array-CGH

Focus::CLL™ NGS Panel:
NOTCH1, SF3B1, TP53, BIRC3, ATM, MYD88, & CARD11

TP53 Mutation Analysis

This work up is intended as a guide for the comprehensive suite of diagnostic tests included in CLL Complete™ to diagnose and monitor CLL. Physicians can order tests individually or allow CGI pathologists and directors to determine a panel evaluation as determined necessary.

Specimen Requirements

	Test	TAT (Mon.-Fri.)	Tissue	Shipping Requirements
Morph. & IHC	**Morphology**	2-4 days	1 **Green**/NaHeparin **or** 1 **Lavender**/EDTA tube PB or BM (2 ml) or FFPE tissue block* or 0.5 cm^3 fresh tissue in RPMI	PB/BM: room tempearture FFPE: room temperature Fresh Tissue: on ice
	B-Cell Lymphoma Panel	2-4 days		
Flow	**CD38**	1-2 days	1 **Green**/NaHeparin **or** 1 **Lavender**/EDTA tube PB or BM (2 ml) or 0.5 cm^3 fresh tissue in RPMI	PB/BM: room tempearture Fresh Tissue: on ice
	ZAP-70	1-2 days		
	MRD-CLL	1-2 days	1 **Green**/NaHeparin **or** 1 **Lavender**/EDTA tube PB (10 ml) or BM (3 ml)	Room temperature
Molecular Diagnostics	**Focus::CLL™ NGS Panel**	10-14 days	1 **Lavender**/EDTA tube PB or BM (2-3 ml)	Room temperature
	MatBA®-CLL/SLL	3-5 days	1 **Lavender**/EDTA tube PB or BM (2-3 ml) or FFPE tissue block* (>70% tumor) or 0.2 cm^3 fresh tissue (>50% tumor) in RPMI	PB/BM: 4°C FFPE: room temperature Fresh Tissue: on ice
	***IGHV* Mutation**	7-10 days		
	***TP53* Mutation**	5-7 days		
	***NOTCH1* Mutation**	7-10 days		
	***SF3B1* Mutation**	10-14 days		
FISH	**FISH Panel**	3-5 days PB/BM 5-7 days tissue	1 **Green**/NaHeparin tube PB or BM (3-5 ml) or FFPE tissue block* or 0.5 cm^3 fresh tissue in RPMI	PB/BM: room tempearture FFPE: room temperature Fresh Tissue: on ice
	Karyotype	5-7 days		
CLL Complete™ Panel		10-14 days	1 **Green**/NaHeparin **and** 1 **Lavender**/EDTA tube PB or BM (8-10 ml); FFPE tissue block* or 0.5 cm^3 fresh tissue in RPMI	PB/BM: room tempearture FFPE: room temperature Fresh Tissue: on ice

* If FFPE tissue block is not available, fifteen 3-5 µm unstained slides are also acceptable. PB: peripheral blood BM: bone marrow FFPE: formalin-fixed paraffin-embedded

CGI Laboratory 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), California (COS 00800558).

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