Chronic Lymphocytic Leukemia Prognostic Markers

Indications for Ordering

Use to determine risk group in newly diagnosed chronic lymphocytic leukemia (CLL)

- *IGHV* mutation
- CD38 expression

Test Description

- *IGHV* Mutation Analysis by Sequencing
  - Polymerase chain reaction/sequencing using VH leader and JH primers
  - Identified clonal VH sequences are searched against a known database for homology
    - Percent of homology to germline sequences is reported
  - CLL clones comprising at least 50% of total B cells can be analyzed
- Leukemia/Lymphoma Phenotyping by Flow Cytometry
  - CD38 expression

Tests to Consider

Primary tests

IGHV Mutation Analysis by Sequencing 0040227

- Determine risk group in newly diagnosed CLL

Leukemia/Lymphoma Phenotyping by Flow Cytometry 2008003

- Aid in evaluation of hematopoietic neoplasms
- Expression of CD38 typically performed for CLL diagnosis and followup

Related tests

Cytogenomic SNP Microarray – Oncology 2006325

- Preferred test at time of diagnosis for detecting prognostically important genomic abnormalities in leukemias/lymphomas and solid tumors involving
  - Loss/gain of DNA
  - Loss of heterozygosity (LOH)
- Monitor disease progression and response to therapy

Chromosome FISH, CLL Panel 2002295

- Alternate test to detect prognostically important genomic abnormalities in CLL
  - Not as sensitive as SNP microarray
- Includes *ATM* (11q22.3), chromosome 12 centromere (Trisomy 12), (D13S319) 13q14.3, p53 (17p13.1)

Disease Overview

Treatment issues

- CLL is a heterogenous disease
  - Therapy based on risk group stratification
  - Clinical course is variable
    - ~1/2 are aggressive, others are indolent
- Cytogenetic, molecular, and flow cytometry testing play an important role in prognostication of CLL

Significance of markers

- *IGHV*
  - *IGHV* mutation status of CLL tends to remain constant over course of disease
  - del(17p) and/or del(11q) correlate with nonmutated *IGHV* genes
  - Presence of mutation associated with more indolent course
- CD38 expression
  - Transmembrane glycoprotein modulates intracellular signaling
  - Cases that express CD38 often have nonmutated *IGHV* genes
  - May reflect an increased proliferative status of CLL
  - Expression levels may vary over course of disease

Test Interpretation

Results

IGHV mutation

- Nonmutated *VH* segment
  - ≥98% identical to the most closely matched germline *VH* gene sequence
  - Associated with unfavorable outcome
- Mutated *VH* segment
  - <98% identical to the most closely matched germline *VH* gene sequence
  - Associated with favorable outcome
  - Borderline mutation
    - 97-97.9% identical to the most closely matched germline *VH* gene sequence
    - May have an intermediate clinical outcome (Hamblin TJ, Br J Hematology, 2008)
- Expression of *VH3-21* segment typically has an unfavorable outcome regardless of mutation status

CD38 expression

- Associated with unfavorable outcome

Limitations

IGHV mutation

- Samples that do not yield amplification product may
  - Contain too few CLL cells (<50% B cells)
  - Express *VH* genes with high numbers of mutations that may compromise clonal B-cell amplification
- Not intended to detect minimal residual disease