Chronic Lymphocytic Leukemia by FISH

Indications for Ordering

Prognostically stratify chronic lymphocytic leukemia (CLL) patients into risk groups
• For individuals who have been diagnosed with CLL by clinical criteria
  o Lymphocytosis of greater than 5x10^9 cells/μL
  o >50% mature-appearing lymphocytes
  o Characteristic immunophenotype of CD5, CD19, CD20, and CD23 expression, monoclonal kappa or lambda expression, and dim surface immunoglobin expression

Test Description
• FISH probes for
  o ATM (11q22.3)
  o Chromosome 12 centromere (trisomy 12)
  o D13S319 (13q14.3)
  o p53 (17p13.1)
• Blood or bone marrow specimens
• 200 nuclei evaluated/probe
• Results compared to samples from 20 control individuals (normal karyotypes, no hematologic diseases)

Tests to Consider

Primary tests
Chromosome FISH, CLL Panel 2002295
• Alternate test to detect prognostically important genomic abnormalities in CLL

Cytogenomic SNP Microarray – Oncology 2006325
• Preferred test at time of diagnosis for detecting prognostically important genomic abnormalities in leukemias/lymphomas and solid tumors involving
  o Loss/gain of DNA
  o Loss of heterozygosity (LOH)
• Monitor disease progression and response to therapy

Related tests
Leukemia/Lymphoma Phenotyping by Flow Cytometry 2008003
• Aid in evaluation of hematopoietic neoplasms
• Expression of CD38 typically performed for CLL diagnosis and followup

IGHV Mutation Analysis by Sequencing 0040227
• Determine risk group in newly diagnosed CLL

Disease Overview

Prevalence – CLL is the most common form of adult leukemia in the Western world

Prognostic issues
• Highly variable clinical course
  o Life span of a few months post diagnosis to >20 years
  o “Watch and wait” approach used for many patients
• Current clinical staging systems (Rai, Binet) do not accurately predict the clinical course of disease if tumor burden is low at time of diagnosis
  o Molecular markers are predictive for many patients
• Predictors of survival
  o Genomic gains and losses (cytogenetic testing using FISH, genomic microarray)
    ▪ Median survival time for the 5 major prognostic groups
      • p53 deletion – 32 months
      • ATM deletion – 79 months
      • Normal FISH – 111 months
      • Trisomy 12 – 114 months
      • 13q14 monoallelic deletions – 133 months
  o IGHV mutation status (molecular testing)
  o Surface CD38 expression (flow cytometry)
• FISH can detect the most common genomic abnormalities in CLL
  o Abnormalities include
    ▪ Trisomy 12
    ▪ Unbalanced rearrangements involving 14q32
    ▪ Deletions of 13q14, 6q21, 17p, and 11q22-23
    ▪ Copy number imbalances across the genome
• Genomic microarray may be considered as an alternative to FISH for detection of genomic gains and losses
  o Microarray has the added benefit of detection of
    ▪ Most common aberrations in CLL
    ▪ Copy number imbalances across the genome
• Using higher numbers of probes may increase sensitivity of test
Structure/function

• Tumor suppressors
  o del(17p) typically involves TP53 locus
  o del(11q) contains ATM gene
• Loss of p53 function or its activator, the ATM gene, is associated with treatment resistance and clinically aggressive disease
• del(17p) and/or del(11q) correlate with nonmutated IGHV genes
• Karyotypic evolution may occur over course of disease

Test Interpretation

Positive results – chromosomal aberration detected

• Least favorable outcome
  o del(17p), followed by del(11q), then trisomy 12q
• Favorable outcome
  o del(13q)
  o Normal diploid karyotype

Limitations

• Panel only detects prognostically important imbalances (gain or loss of DNA) in the chromosomes of interest
• Chromosome alterations outside the regions complementary to these FISH probes will not be detected
• Ideal testing is when significant disease is present