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
  - Lymphocytosis of greater than $5x10^9$ cells/µL
  - >50% mature-appearing lymphocytes
  - Characteristic immunophenotype of CD5, CD19, CD20, and CD23 expression, monoclonal kappa or lambda expression, and dim surface immunoglobin expression

Test Description

- FISH probes for
  - ATM (11q22.3)
  - Chromosome 12 centromere (trisomy 12)
  - D13S319 (13q14.3)
  - p53 (17p13.1)
- Blood or bone marrow specimens

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
  - Loss/gain of DNA
  - Loss of heterozygosity (LOH)
- Monitor disease progression and response to therapy

Related Tests

Leukemia/Lymphoma Phenotyping Evaluation by Flow Cytometry 3001780

- 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
  - Life span of a few months post diagnosis to ≥20 years
  - "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
  - Molecular markers are predictive for many patients
- Predictors of survival
  - Genomic gains and losses (cytogenetic testing using FISH, genomic microarray)
    - Median survival time for the five major prognostic groups
      - p53 deletion – 32 months
      - ATM deletion – 79 months
      - Normal FISH – 111 months
      - Trisomy 12 – 114 months
      - 13q14 monoallelic deletions – 133 months
  - *IGHV* mutation status (molecular testing)
  - Surface CD38 expression (flow cytometry)
- FISH can detect the most common genomic abnormalities in CLL
  - 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
  - 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

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Structure/Function

- Tumor suppressors
  - del(17p) typically involves TP53 locus
  - 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
  - del(17p), followed by del(11q), then trisomy 12q
- Favorable outcome
  - del(13q)
  - 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

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