Acute Myelogenous Leukemia with Myelodysplastic Syndrome (MDS) or Therapy-Related MDS Panel by FISH

Indications for Ordering

Diagnosis in conjunction with cytogenetics for individuals with suspected therapy-related MDS

Test Description

Fluorescence in situ hybridization (FISH)

- Performed on bone marrow cells using unstimulated cultures either from direct harvest or 24-hr culture
  - Peripheral blood can be used but is not preferred
- Probes
  - -5/del(5q)
  - -7/del(7q)
  - 11q23 rearrangements
    - Targets *MLL*
- Each probe can be run as part of the panel or individually

Tests to Consider

Primary Test

Acute Myelogenous Leukemia (AML) with Myelodysplastic Syndrome (MDS) or Therapy-Related AML, by FISH 2002653

- Use in conjunction with conventional cytogenetics for diagnosis, prognosis, and monitoring in therapy-related MDS or AML associated with MDS

Related Tests

Chromosome Analysis, Bone Marrow 2002292

- Diagnosis, prognosis, and monitoring of MDS and/or AML

Chromosome Analysis, Bone Marrow with Reflex to Genomic Microarray 2007130

- Diagnosis, prognosis, and monitoring of MDS
- If chromosome analysis is “normal” or “no growth,” then genomic microarray testing will be added

Cytogenomic SNP Microarray – Oncology 2006325

- Preferred test for fresh specimens 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, Interphase 2002298

- Specific FISH probes must be requested and include:
  - -5/del(5q)
  - -7/del(7q)
  - +8
  - del(20q)
  - *MLL* rearrangements (11q23)
  - *EVI1* rearrangements [inv(3) or t(3;3)]
  - *RUNX1-RUNX1T1* fusion t(8;21)
  - *PML-RARA* fusion t(15;17)
  - *CBFB* inv(16) or t(16q)

Myelodysplastic Syndrome (MDS) Panel by FISH 2002709

- Use in conjunction with conventional cytogenetics for diagnosis, prognosis, and monitoring of MDS

Acute Myeloid Leukemia Mutation Panel by Next Generation Sequencing 3002714

- Use to assess for single gene mutations, including substitutions and smaller insertions and deletions, that may have prognostic and/or therapeutic significance in AML

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117

- Use to assess for single gene mutations, including substitutions and insertions and deletions that may have diagnostic, prognostic, and/or therapeutic significance

Disease Overview

- Myelodysplastic disorders are clonal hematopoietic malignancies characterized by:
  - Ineffective hematopoiesis
  - Cytopenia
  - Unilineage or multilineage dysplasia
  - Increased susceptibility to leukemic transformation
- 10-15% of MDS follows treatment with chemotherapy or radiation

AML with Myelodysplasia-Related Change

- Represents 25-30% of AML cases
- Elderly individuals predominate
- Generally presents with pancytopenia
- Chromosome abnormalities are similar to those found in MDS unrelated to cytotoxic agents
  - Often involve gain or loss of major segments of specific chromosomes with complex karyotypes

Treatment-Related Myeloid Neoplasms

- Late complication of cytotoxic or radiation therapy
  - Rate of development does not differ between those with a hematologic versus solid malignancy
- Accounts for 10-20% of all AML, MDS, and MDS/myeloproliferative neoplasms (MPN)
- 90% have clonal chromosomal abnormality
  - Often complex
  - Similar to those observed in AML with myelodysplasia-related change
- Disease differs based on type of therapy (alkylating agent/radiation versus topoisomerase II)
  - Individual may have received both therapies at some point in their illness, meaning either presentation can occur
  - t-MDS/t-AML arising after alkylating agent and/or radiation therapy
    - 80-85% of treatment-related myeloid neoplasms
    - Latency period 3-7 years (median 5 years)
    - Initial presentation: MDS with trilineage dysplasia
    - Cytogenetics (most common)
      - Abnormalities of chromosomes 5, 7, or complex karyotypes
  - t-AML/t-MDS arising after topoisomerase II inhibitor therapy
    - ~15% of treatment-related myeloid neoplasms
    - Latency period 2-3 years
    - Initial presentation: AML (typically no antecedent MDS)
    - Cytogenetics
      - Balanced translocations
      - *MLL* rearrangements
      - t(15;17)
      - inv (16)
  - Therapy-related myeloid neoplasms have a significantly worse outcome than do their de novo counterparts
    - Exceptions are t-AML with inv(16) or t(15;17)

Diagnostic Criteria

- AML with myelodysplasia-related changes
  - ≥20% blood or marrow blasts AND
    - Previous history of MDS OR
    - MDS-related cytogenetic abnormality OR
    - Multilineage dysplasia
      - Dysplasia in at least 50% of cells in 2 or more hematopoietic lineages
  - Absence of cytogenetic abnormalities described in AML with recurrent genetic abnormalities
  - No history of prior cytotoxic therapy for an unrelated disease
- Therapy-related myeloid neoplasms (t-MDS, t-MDS/MPN, or t-AML)
  - Myeloid neoplasms (excluding MPNs) that arise as a consequence of cytotoxic or radiation therapy
  - May be subdivided by blast count but behaves as a single biologic disease

Diagnostic Issues

- MDS associated with AML or cytotoxic therapy has a poor prognosis which is related to cytogenetic abnormalities
- FISH
  - Detects specific genomic aberrations not detected by cytogenetics (eg, cryptic rearrangements)
  - Aids in classification of disease risk in MDS for therapy decisions

See Revised International Prognostic Scoring System (IPSS-R) (Greenberg, Blood 2012) below for risk stratification

Genetics

Gene: *MLL*

Structure/Function

- Maps to 11q23
- Transcriptional regulatory factor
- Multiple translocation partners
- Most common translocations
  - t(9;11)(p22;q23)
  - t(11;19)(q23;p13)

Test Interpretation

Analytical Sensitivity/Specificity: >95%

- Limit of detection is probe dependent: ~1-5% in interphase nuclei

Results

- Normal: no -5/del(5q31), -7/del(7q31), or 11q23 rearrangement detected
- Abnormal: genetic abnormality detected
  - -5/del(5q)
    - Poor prognosis
  - -7/del(7q)
    - Poor prognosis
  - t(11q23:var)
    - Generally associated with poor prognosis

Limitations

- *MLL* gene at 11q23 has multiple translocation partners which are not identified by this test
- Panel detects only the specific aberrations targeted by the probes