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

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117

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