Myelodysplastic Syndrome Panel by FISH

Indications for Ordering

- Aid in diagnosis and risk stratification of myelodysplastic syndrome (MDS) in conjunction with cytogenetics
  - Most useful at diagnosis following a failed or suboptimal standard cytogenetic study (<20 metaphases available)
- May aid in identifying individuals with MDS who could benefit from lenalidomide
  - With abnormal karyotype involving chromosome 5 and corresponding morphologic features

Test Description

Fluorescence in situ hybridization

- Performed on bone marrow (BM) cells using unstimulated cultures either from direct harvest or 24-hour culture
  - Peripheral blood can be used but is not preferred due to lowered clinical sensitivity
- Probes
  - del(5q)
  - -7/del(7q)
  - +8
  - del(20q)
- Each probe can be run as part of the panel or individually

Tests to Consider

Primary test

Myelodysplastic Syndrome (MDS) Panel by FISH 2002709

- Diagnosis and prognosis of MDS
  - Most useful at diagnosis following a failed or suboptimal standard cytogenetic study (<20 metaphases available)
  - Includes four probes – del(5q), -7/del(7q), +8, and del(20q)

Related tests

Chromosome Analysis, Bone Marrow 2002292

- Diagnosis, prognosis, and monitoring of MDS

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

- Detects genomic abnormalities that may have diagnostic, prognostic, and/or therapeutic significance in leukemias/lymphomas and solid tumors, including
  - Loss/gain of DNA
  - Loss of heterozygosity (LOH)
- Cannot detect balanced chromosomal rearrangements (translocations and inversions)
- May be performed on BM, peripheral blood, or solid tumor tissues

Myeloid Malignancies Somatic Mutation and Copy Number Analysis Panel 2012182

- Includes both Cytogenomic SNP Microarray and Myeloid Malignancies Mutation Panel by Next Generation Sequencing
- Detects genetic and genomic abnormalities in myeloid disease that may have diagnostic, prognostic, and/or therapeutic significance, including
  - Loss/gain of DNA
  - Loss of heterozygosity (LOH)
  - Single gene mutations (substitutions, small insertions and deletions)
- May be performed on BM or peripheral blood

Chromosome FISH, Interphase 2002298

- Diagnosis, prognosis, and monitoring of MRD in MDS
- Specific FISH probes must be requested and include
  - del(5q)
  - -7/del(7q)
  - +8
  - del(20q)
  - 11q23 *KMT2A(MLL)* rearrangement
  - inv(3) or t(3;3) *RPN1-MECOM(EVI1)* fusion
  - 21q22 *RUNX1* loss/gain/rearrangement

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

- Diagnosis and prognosis in therapy-related MDS and AML
- Probes
  - del(5q)
  - -7/del(7q)
  - 11q23 *KMT2A(MLL)* rearrangement

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
- May be performed on BM or peripheral blood

Disease Overview

Diagnostic criteria (WHO 2008; International Working Group, 2007)

- Peripheral blood findings – cytopenia (hemoglobin <10g/dL, ANC <1.8X109/L, platelets <100X10^9/L), variable presence of blasts <20%, Auer rods ±, monocytes <1x10^9/L, platelets low, normal, or increased
- BM findings – dysplasia ≥10% in one or more myeloid lineage, blast count <20%, Auer rods ±, presence of ring sideroblasts ± and % defines subtypes, presence of specific cytogenetic abnormalities (a subset is considered presumptive evidence in absence of definitive morphologic criteria)
- Diagnosis of presumptive MDS is allowed in individuals with refractory cytopenia(s) who lack definitive morphologic criteria if specific cytogenetic abnormalities are detected
  - Some clonal cytogenetic abnormalities are not included (eg, -Y, +8 or del(20q) as the sole abnormality)
- Exclusion of other disorders as etiology for dysplasia and/or cytopenia

Diagnostic issues

- Diagnosis of MDS is often difficult and may require combination testing (eg, cytogenetics, FISH, microarray and/or mutation testing)
- FISH
  - Aids in classification of disease risk in MDS for therapy decisions
  - See Revised International Prognostic Scoring System (IPSS-R) (Greenberg, Blood 2012) below for cytogenetic risk stratification
  - Aids in monitoring for MRD
  - May detect specific genomic aberrations not detected by cytogenetics (eg, cryptic rearrangements)
  - Has limited clinical utility following a normal 20-cell CC study

Test Interpretation

Analytical sensitivity/specificity – >95%

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

Results

- Normal
  - No evidence of del(5q), -7/del(7q), +8, or del(20q)
- Abnormal – genetic abnormality detected
  - del(5q)
    - Good prognostic subgroup when isolated or combined with any other single abnormality except -7 (WHO update in progress)
    - Defines a unique MDS subtype with corresponding morphologic features
    - Presumptive evidence of MDS in the absence of definitive morphologic criteria
  - -7/del(7q)
    - -7
      - Poor prognostic subgroup when isolated or combined with any other single abnormality
    - del(7q)
      - Intermediate prognostic subgroup when isolated
      - Poor prognostic subgroup when combined with any other single abnormality
    - Presumptive evidence of MDS in the absence of definitive morphologic criteria
  - +8
    - Intermediate prognostic subgroup when isolated or combined with any other single abnormality
  - del(20q)
    - Good prognostic subgroup when isolated

Limitations

Panel detects only the specific aberrations targeted by the probes

Cytogenetic Prognostic Scoring System Used in IPSS-R			
Prognostic subgroup	**Cytogenetic Abnormality**		
	Single	**Double**	**Complex**
Very good	del(11q); -Y	----------	----------
Good	Normal; del(5q); del(12p); del(20q)	del(5q) combined with another abnormality	----------
Intermediate	del(7q); +8; i(17q); +19; +21; any other independent clones	Any other abnormality in combination	----------
Poor	inv(3)/t(3q)/del(3q); -7	-7/del(7q) combined with another abnormality	3 abnormalities
Very poor	----------	----------	>3 abnormalities