

AML with MDS or Therapy-Related MDS Panel by FISH

DETECTION OF SPECIFIC RECURRENT GENOMIC ABERRATIONS IN THERAPY-RELATED MYELODYSPLASTIC SYNDROME (T-MDS) OR ACUTE MYELOID LEUKEMIA ARISING FROM MYELODYSPLASTIC SYNDROME BY FLUORESCENCE IN SITU HYBRIDIZATION (FISH)

Test Highlights

- This test provides significant prognostic information for patients with AML arising in the setting of previous MDS, or patients with therapy-related MDS/AML.
- FISH may detect specific genomic aberrations that are not detected by cytogenetics.
- This test aids in monitoring response to therapy or progression of the disease.

Clinical Background

- Myeloproliferative disorders are clonal hematopoietic malignancies characterized by ineffective hematopoiesis, cytopenia, unilineage or multilineage dysplasia, and susceptibility to leukemia. They are most common in adults, particularly in the elderly population, and the incidence in males is twice that in females. 10–15 percent of MDS occurs following treatment with chemotherapy and radiation (therapy-related MDS, t-MDS).
- Classification of MDS and AML is based on bone marrow histology, cytochemical and immunophenotypic features, and cytogenetic findings. Genetic studies are required at diagnosis not only for identifying specific genetic abnormalities but also for monitoring disease progression.
- Recurrent cytogenetic abnormalities observed in t-MDS or t-AML include:
 - Monosomy 7: observed in over half of cases; associated with a poor prognosis.
 - Deletion(7q): observed in 5–10 percent of cases; associated with a poor prognosis.
 - Deletion(5q): associated with a favorable prognosis if present as a sole abnormality.
 - 11q23 rearrangements involving *MLL*: often observed in MDS following treatment with anti-topoisomerase II (epidophyllotoxins); associated with a poor prognosis.
- The International Prognostic Scoring System (IPSS) was developed by the Myelodysplastic Syndrome Working Group to predict survival in patients with MDS. This system combines information on bone marrow blast percentage, cytogenetic abnormalities, and type(s) of cytopenia into low, intermediate-1, intermediate-2, and high-risk disease. In this system, cytogenetic abnormalities are classified as follows:
 - Good risk: normal karyotype, isolated del(5q), isolated del(20q), and -Y.
 - Poor risk: Abnormalities of chromosome 7 or complex karyotype with three or more abnormalities.
 - Intermediate risk: all other abnormalities.

- Standard chromosome analysis using metaphase cells requires dividing cells and remains the gold standard for the detection of cytogenetic abnormalities. However, cytogenetically visible rearrangements can sometimes be missed due to suboptimal chromosome morphology, lack of dividing neoplastic cells, or preferential growth of normal cells in culture.
- In a diagnostic cytogenetics laboratory, FISH analysis has several advantages over chromosome studies. It has a rapid turnaround time, detects small numbers of abnormal cells, and can also be performed on non-dividing (interphase) cells. In addition, FISH can detect cryptic or subtle rearrangements that might be difficult to detect by routine karyotyping.

Indications for Ordering

- For patients with MDS progressing to AML.
- Myeloid dysplasia in patients with previous chemotherapy or radiation therapy.
- FISH testing is indicated at the time of diagnosis for proper classification. However, it may also be used for follow-up studies, either to monitor response to therapy or progression of the disease.

Additional Ordering Notes

- A sodium-heparin (green-top) tube with 3–4 mL of bone marrow is required.
- Samples should be stored at room temperature and transported to the laboratory within 24 hours of draw.

Methodology

- Bone marrow cells on unstimulated cultures either from direct harvest or 24-hour culture are analyzed by FISH using a set of commercially available FISH probes.
- Each probe can be run as a part of the panel or individually.
- The FISH probes for del(5q), del(q)/monosomy 7, and *MLL* (11q23) are set up separately for each patient.

- Hybridization and detection of hybridization signals are performed according to the manufacturer's protocols.
- At least two technologists score each case.
- 200 nuclei are evaluated, for each probe.
- Bone marrow samples from 20 individuals without apparent hematological diseases and with normal karyotype are used as controls for each probe to determine the cutoff value for normal variation of the probe signal patterns.

Limitations

- This probe panel only detects specific aberrations in the chromosomes of interest for diagnosis and prognosis.
- Chromosome alterations outside the regions complementary to these FISH probes will not be detected.

Tests Available

FISH panel for myelodysplastic syndrome:

	Chromosome Abnormalities	Probe Names (Genes involved)	Probe Type
1.	Deletion 5q	D5S23, D5S721 as control (<i>EGR1</i>)	Dual color
2.	Deletion 7q/ monosomy 7	D7Z1/D7S486	Dual color
3.	<i>MLL</i> (11q23 rearrangement)	<i>MLL</i>	Breakapart

References

1. Myelodysplastic syndromes. In *Cancer Cytogenetics*, 3rd ed. S Heim and F Mitelman, eds. 2009; Hoboken, NJ: Wiley-Blackwell.
2. Swerdlow SH, et al. 2008. *WHO classification of tumours of haematopoietic and lymphoid tissues*, 4th ed. Lyon, France: International Agency for Research on Cancer.

Test Information

2002653

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

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.