

Myeloproliferative Disorder (MPD) Panel by FISH

DETECTION OF SPECIFIC RECURRENT GENOMIC ABERRATIONS IN MYELOPROLIFERATIVE DISORDER (MPD) BY FLUORESCENCE IN SITU HYBRIDIZATION (FISH)

Test Highlights

- This test allows for the diagnosis of and provides significant prognostic information for MPDs with eosinophilia. It is suitable for widespread use.
- Hematopoietic neoplasms that can be detected by using this test are chronic myelogenous leukemia (CML), as well as myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, and *FGFR1*.
- FISH is more sensitive than conventional cytogenetics in detecting these specific genomic aberrations.
- This test aids in monitoring response to therapy or progression of disease.

Clinical Background

- Myeloproliferative disorders are clonal hematopoietic malignancies and are characterized by proliferation of one or more myeloid lineages (i.e., granulocytic, erythroid, megakaryocytic, mast cells) in the bone marrow. They are most common in adults.
- Classification of MPD is based on cell of origin and morphology, as well as cytochemical and immunophenotypic features. Genetic studies are required at diagnosis not only for identifying specific genetic abnormalities but also for monitoring disease progression.
- Identification of specific recurrent chromosomal abnormalities plays an important role in the diagnosis of MPD and also provides significant prognostic information. For example, patients with rearrangements of *BCR/ABL*, *PDGFRA*, and *PDGFRB* can respond to tyrosine kinase inhibitors such as imatinib. Patients with *FGFR1* rearrangements do not respond to imatinib.
- Types of MPD with recurrent genetic changes:
 - Chronic myelogenous leukemia, *BCR/ABL* fusion positive.
 - Myeloid and lymphoid neoplasm with eosinophilia and *PDGFRA* rearrangement at 4q12.
 - Myeloid neoplasm with eosinophilia and *PDGFRB* rearrangement at 5q33.
 - Myeloid and lymphoid neoplasm with *FGFR1* rearrangement, also known as 8p11 myeloproliferative syndrome (EMS).
- Standard chromosome analysis using metaphase cells requires dividing cells and remains the gold standard for the detection of cytogenetic abnormalities. However, MPD with *PDGFRA* rearrangements could be a result of cryptic/submicroscopic deletion at chromosome 4q12 and cannot be detected by karyotyping. In 5 percent of CML, t(9;22) (i.e., *BCR/ABL* rearrangements) can be cryptic and undetectable using standard cytogenetic techniques. Cytogenetically visible rearrangements can sometimes be missed due to suboptimal chromosome morphology, lack of dividing neoplastic cells, or selection for 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 nondividing (interphase) cells. In addition, FISH can detect cryptic or subtle rearrangements that might be difficult to detect by routine karyotyping.
- FISH using breakapart probes is a useful test in leukemia with variant rearrangements. These FISH probes target the critical genes that can have multiple translocation partners and can detect the rearrangement regardless of the translocation partner. However, to identify the translocation partner correlation with chromosome studies is recommended. The tri-color dual-fusion FISH probe set for *BCR/ABL* not only detects the translocations, insertions, or cryptic rearrangements between chromosomes 9 and 22 that lead to *BCR/ABL* fusions, but can also detect deletions on derivative 9 or derivative 22 and differentiate between real and coincidental fusions signals.

Indications for Ordering

- Clinical indication encompasses a wide spectrum of myeloproliferative/ lymphoproliferative neoplasms with eosinophilia.
- FISH testing is indicated at the time of diagnosis for proper classification. It may be also 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 t(9;22), rearrangements of *PDGFRA* at 4q12, *PDGFRB* at 5q33, and *FGFR1* at 8p12 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 the same case.
- For each probe, 200 nuclei are evaluated.
- 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.

- FISH Panel for myeloproliferative neoplasms:

	Chromosome abnormalities	Probe names (Genes involved)	Probe type
1.	t(9;22)(q34;q11.2)	<i>BCR/ABL</i>	Tricolor dual fusion
2.	4q12 rearrangement	<i>PDGFRA</i>	Tricolor rearrangement
3.	5q33*	<i>PDGFRB</i>	Breakapart
4.	8p11*	<i>FGFR1</i>	Breakapart

*The *PDGFRB* gene on 5q33 and *FGFR1* on 8p11 have multiple translocation partners. FISH breakapart probes for *PDGFRB* and *FGFR1* can only detect rearrangements of *PDGFRB* and *FGFR1* and do not identify the translocation partners.

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

References

1. Chromosomal and molecular genetic aberrations of tumor cells. In *Cancer cytogenetics*, 3rd ed. S Heim and F Mitelman, eds. 2009; Hoboken, New Jersey: 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

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Myeloproliferative Disorders Panel 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.