

Eosinophilia Panel by FISH

Test Highlights

- This test allows for diagnosing or providing significant prognostic information in patients with acute or chronic leukemia with eosinophilia and is suitable for widespread use.
- In acute myeloid leukemia (AML) or chronic myeloproliferative neoplasms with eosinophilia, specific recurrent genetic changes can be detected by using this test. These genetic abnormalities include *inv(16)/t(16;16)* and rearrangements of *PDGFRA*, *PDGFRB*, and *FGFR1*.
- FISH is more sensitive than conventional cytogenetics in detecting these specific genomic aberrations.
- This test may also be used to monitor response to therapy or progression of the disease.

Clinical Background

- Myelomonocytic acute myeloid leukemia with abnormal marrow eosinophils is frequently associated with the recurrent cytogenetic abnormality *inv(16)/t(16;16)* and has been reported in all age groups, with predominance in males.
- Myeloproliferative neoplasms (MPN) 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 common in adults.
- Classification of MPN and AML with *inv(16)* or *t(16;16)* 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.
- Recurrent specific chromosome abnormalities have played an important role in the diagnosis of MPN and AML with *inv(16)* or *t(16;16)*. They also provide significant prognostic information and may affect chemotherapeutic approach. Genetic classification is important in this group of disorders, as patients with *PDGFRA* and *PDGFRB* rearrangements can respond to tyrosine kinase inhibitors such as imatinib. It is not yet clear if patients with *FGFR1* rearrangements respond to tyrosine kinase inhibitors.
- Recurrent genetic abnormalities associated with eosinophilia and/or abnormal marrow eosinophils:
 - AML with *inv(16)(p13.1;q22)* or *t(16;16)(p13.1;q22)*–(*MYH11/CBFB*).
 - 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 at 8p11; 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, MPN with *PDGFRA* rearrangement could be a result of cryptic/submicroscopic deletion at chromosome 4q12 and cannot be detected by karyotyping. In AML with *inv(16)* or *t(16;16)* (i.e., *CBFB*), rearrangement 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 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. FISH using breakapart probes is a useful test in diseases with variant rearrangements. Breakapart FISH probes target the critical gene that has multiple translocation partners and can detect the rearrangement of the critical gene regardless of the translocation partner. However, to identify the translocation partner, correlation with chromosome studies is recommended.

Indications for Ordering

- Clinical indication encompasses a wide spectrum of myeloid neoplasms presenting with eosinophilia.
- FISH testing is indicated at the time of diagnosis for proper classification. 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.

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.

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 panel or individually.
- The FISH probes 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.
- 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.
- Tests available
 - FISH Panel for MPN with Recurrent Genetic Abnormalities:

Chromosome Abnormalities	Probe Names (Genes Involved)	Probe Type
1. Inv(16)/t(16;16)	<i>CBFB</i> rearrangement	Breakapart
2. 4q12 rearrangement	<i>PDGFRA</i> rearrangement	Tricolor rearrangement
3. 5q33*	<i>PDGFRB</i> rearrangement	Breakapart
4. 8p11*	<i>FGFR1</i> rearrangement	Breakapart

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

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

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