

# Myeloproliferative Neoplasms (MPN) Panel by FISH

## *DETECTION OF SPECIFIC RECURRENT GENOMIC ABERRATIONS IN MYELOPROLIFERATIVE NEOPLASMS (MPN) BY FLUORESCENCE IN SITU HYBRIDIZATION (FISH)*

### Test Highlights

- This test aids with the diagnosis of myeloproliferative neoplasms (MPN) with eosinophilia, and it provides significant prognostic information for patients with these disorders. 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 rearrangements of the *PDGFRA*, *PDGFRB*, and *FGFR1* genes.
- FISH is more sensitive than conventional cytogenetics in detecting these specific genomic aberrations.
- This test aids with monitoring response to therapy and/or progression of disease.

### Clinical Background

- Myeloproliferative neoplasms are clonal hematopoietic malignancies and are characterized by proliferation of one or more myeloid lineages (i.e., granulocytic, erythroid, megakaryocytic, and mast cells) in the bone marrow. They are most common in adults.
- Classification of MPN is based on cell of origin and cell morphology, as well as cytochemical and immunophenotypic features. Genetic studies are required for 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 MPN and also provides significant information about prognosis. For example, patients with rearrangements of the *BCR/ABL*, *PDGFRA*, and *PDGFRB* genes can respond to tyrosine kinase inhibitors, such as imatinib. Patients with mutations of the *FGFR1* gene do not respond to imatinib.
- Types of MPN 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 analysis of cultured, dividing cells. However, MPN with *PDGFRA* rearrangements could be a result of cryptic/submicroscopic deletion at chromosome 4q12, which cannot be detected by karyotyping. In 5% of patients with 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 (hence, a lower frequency) 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.

- FISH using break-apart probes is a useful test in leukemia with variant rearrangements of specific genes. These FISH probes target the critical genes that can have multiple translocation partners, and the probes can detect the rearrangement regardless of the translocation partner. However, the use of chromosome studies to identify the translocation partner correlation is recommended. The tricolor, 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 it can also detect deletions on derivative 9 or derivative 22, and it can differentiate between real and coincidental fusions signals.

### Indications for Ordering

- Suspicion of myeloproliferative/ lymphoproliferative neoplasms 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.

### 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 either 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 8p11 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, so as to determine the cutoff value for normal variation of the probe-signal patterns.

### Limitations

Chromosome alterations outside the regions complementary to these FISH probes will not be detected.

### Tests available

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 at 5q33 and the *FGFR1* gene at 8p11 have multiple translocation partners. FISH break-apart probes for the *PDGFRB* and the *FGFR1* genes can detect only rearrangements of the *PDGFRB* and the *FGFR1* genes and do not identify the translocation partners.

### References

1. Heim S and Mitelman F, eds. Chromosomal and molecular genetic aberrations of tumor cells. In *Cancer cytogenetics*, 3rd ed. 2009; Hoboken, NJ: Wiley-Blackwell, 209–32.
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

**2002360**

### Myeloproliferative Disorders Panel by FISH

For specific collection, transport, and testing information, refer to the ARUP website at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).

### AUTHORS

Sarah South, PhD

Arthur Brothman, PhD