



**OHSU Molecular Diagnostic Center**  
Shipping Address: 2525 SW 3<sup>rd</sup> Avenue, Suite 350  
Portland, OR 97201

CAP #2442619  
CLIA #38D0881787

Phone: (503) 494-5400  
1-888-375-4636  
Fax: (503) 494-6922

[www.ohsulabs.com](http://www.ohsulabs.com)

## **NEW MOLECULAR MARKERS FOR PROGNOSIS IN ACUTE MYELOID LEUKEMIA**

### **Mutations in the FLT3 &/or Nucleophosmin (NPM1) Genes**

#### **Nucleophosmin (NPM1) Mutations**

- The most common molecular abnormality, present in ~50% of AML's with normal karyotype (nk).
- nk-AML constitutes ~45% of AML's and conveys an "intermediate" (but heterogeneous) prognosis.
- Exon 12 NPM1 mutations (always 4 bp insertions) disrupt a key regulatory region at the C-terminus, and cause abnormal cytoplasmic (not typical nucleolar) localization.
- NPM1 mutations have been shown to impart a FAVORABLE PROGNOSIS – for event-free survival, relapse-free survival, overall survival, and attainment of first complete remission.
- ~40% of AML's with NPM1 mutations also have a FLT3 gene mutation, and the prognosis for these "double-mutation" patients is NOT favorable (ie, FLT3 status "trumps" NPM1 status).

#### **FLT3 Mutations**

- The 2<sup>nd</sup> most common molecular abnormality, present in ~30% of nk-AML's.
- Most common mutation is an internal tandem duplication mutation (ITD) in the juxtamembrane domain (exon 14) of the FLT3 receptor tyrosine kinase.
- ITD mutation creates a constitutively activated, ligand-independent tyrosine kinase.
- FLT3-ITD mutations (regardless of NPM1) have been shown to impart a POOR PROGNOSIS – for event-free survival, relapse-free survival, overall survival, and duration of complete remission.
- FLT3 is a promising experimental therapeutic target for small molecule kinase inhibitors.

#### **Clinical Utility of NPM1 and/or FLT3 mutation status:**

- Poor prognosis FLT3-ITD+ (but not NPM1+) cases may be better candidates for higher-risk treatments, ie, stem cell transplantation.

#### **Testing Methodology**

- NPM1: PCR of exon 12; DNA sequence analysis for insertion mutation.
- FLT3: PCR of exon 14 juxtamembrane domain; ITD detection by denaturing HPLC and/or gel.
- Detection sensitivity ~20% [i.e., mutant clones (blasts) < 20% may be missed].
- Report with qualitative mutation status (present/absent) sent within 1-2 weeks.

#### **Sample Requirements:**

- 5-10 mL of anti-coagulated blood or bone marrow — yellow (ACD) or purple (EDTA) tube
- Transport at room temperature to arrive within 24 hours; if sample cannot arrive within 24 hours, refrigerate (unspun; no freezing), then ship by overnight courier at room temperature.

For more information about this and other tests offered by the Molecular Diagnostic Center go to [www.ohsulabs.com](http://www.ohsulabs.com) or call the phone numbers listed above.