SCHOOL OF MEDICINE
INDIANA UNIVERSITY

**Department of Medical and Molecular Genetics**
**Division of Diagnostic Genomics**

**Laboratory Test Directory**

# *PML/RARA* RNA expression analysis

**CPT Code(s):** 81315, 81316

**Service Code (IU Health):** 53053054

**Ordering Recommendation**: Diagnosis and monitoring of t(15;17) *PML*/*RARA* to aid clinicians in determining follow up procedures and therapeutic strategies for APL

**Synonyms:** Acute promyelocytic leukemia, t(15;17), PML/RARA, bcr1, bcr2, bcr3, quantitative real-time PCR, qualitative RT-PCR, quantitative RT-PCR, polymerase chain reaction, gene expression,

**Methodology:** Reverse transcription quantitative real-time PCR (RT-qPCR)

**Performed:** Weekly

**Reported:** 7-10 days

## Specimen Requirements

**Patient Preparation:** None required for whole blood/bone marrow

**Collect:** Lavender (EDTA) tubes

**Specimen Volume:** Blood: 1-3 mL of whole blood/bone marrow

**Storage/Transport:** Refrigerated/room temperature and should arrive in the laboratory ≤ 24 hours after collection

**Unacceptable Conditions:** Frozen, grossly hemolyzed, clotted, or arrive in the laboratory ≥ 48 hours after collection

**Stability:** 48 hours at 2°C to 8°C; one week at 2°C to 8°C after sample is mixed with 2X DNA/RNA Shield

**Reference Interval:** Limit of detection is $10^{-4}$ (or 0.0001 or 0.01% bcr/*PML*)

## Interpretive Data

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**Characteristics:** Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia (AML), a malignancy of the bone marrow. APL is characterized by accumulation of immature white blood cells (or promyelocytes) in the bone marrow, and decreased normal platelets, white blood cells, and red blood cells in the body. This may lead to abnormal bruising/bleeding, frequent infections, anemia, fatigue, and pale skin. Other symptoms include bone and joint pain, fever, weight loss, and decreased appetite. Molecularly, APL is diagnosed by a translocation involving the promyelocytic leukemia (*PML*) gene on chromosome 15 and the retinoic acid receptor alpha (*RARA*) gene on chromosome 17. The t(15;17)(q24;q21.1) occurs in ≥98% of APL. Three fusion transcript variations, bcr1, bcr2 and bcr3, are generated as a result of different breakpoint cluster regions (bcr) within the *PML* gene. The breakpoint on chromosome 17 is always located within the second intron of the *RARA* gene. The bcr1 (~45% to 55%) variation results from a break within intron 6 of the *PML* gene. The bcr3 (~37% to 45%) variation indicates a breakpoint within intron 3 of the *PML* gene. The bcr2 (~8% to 10%) variation represents the least common *PML* breakpoints, demonstrating inconsistent sites within exon 6 of the *PML* gene and resulting in the fusion of a variable portion of *PML* exon 6 with exon 3 of the *RARA* gene.

**Cause:** The t(15;17)(q24;q21.1) represents >98% of APL. Translocations involving the *RARA* gene on chromosome 17 and other partner genes have been recognized in a few cases of APL.

**Incidence:** APL has an incidence of about 1/250,000. Overall, APL accounts for approximately 10% of cases of AML.

**Analytical sensitivity and specificity:** >99%

**Clinical sensitivity and specificity:** The t(15;17)(q24;q21.1) represents >98% of APL. This assay can detect three fusion transcript variants, bcr1, bcr2, and bcr3.

**Limitations:** Translocations involving breakpoints other than bcr1, bcr2, and bcr3 cannot be detected. Minimal reportable range is $10^{-4}$. Although rare, false positive or false negative results may occur. All results should be interpreted in the context of clinical findings, relevant history, and other laboratory data.

**References:**


1. Health conditions: National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD): The Library; 2017 Apr 18. Acute Promyelocytic Leukemia; [reviewed 2011 Apr; cited 2017 Apr 20]. Available from: https://ghr.nlm.nih.gov/condition/acute-promyelocytic-leukemia.
2. Gallagher RE, et al. Characterization of Acute Promyelocytic Leukemia Cases With PML-RARA Break/Fusion Sites in PML Exon 6: Identification of a Subgroup With Decreased In Vitro Responsiveness to All-Trans Retinoic Acid. *Blood* 1995; 86(4): 1540-1547. PMID:7632962.
3. Choppa PC, et al. A Novel Method for the Detection, Quantitation, and Breakpoint Cluster Region Determination of t(15;17) Fusion Transcripts Using a One-Step Real-Time Multiplex RT-PCR. *Am J Clin Pathol* 2003; 119: 137-144. PMID:12520709.
4. De Angelis F and Breccia M. Molecular Monitoring as a Path to Cure Acute Promyelocytic Leukemia. *Rare Cancers Ther* 2015; 3: 119-132. PMID:27182481.