



## TP53 EXONS 2-11 MUTATION ANALYSIS (TUMOR) TP53 EXONS 2-11 SEQUENCE ANALYSIS (LI-FRAUMENI)

*BloodCenter of Wisconsin's Diagnostic Laboratories offer TP53 mutation analysis for hematologic malignancies and Li-Fraumeni Syndrome*

### BACKGROUND:

The tumor suppressor gene TP53, located at chromosome 17p13.1, codes for the cellular tumor antigen p53. TP53 responds to DNA damage by causing cell cycle arrest and transcriptionally activating genes to repair the DNA or induce apoptosis, thus preventing an abnormal cell from surviving and proliferating. Loss of TP53 function decreases the chance that cells with genetic errors will undergo DNA repair or apoptosis. These damaged cells can proliferate further which can lead to abnormal cells and eventually a malignant tumor (1).

Somatic mutations in TP53 are the most commonly detected genetic aberrations in cancer and are often associated with adverse outcomes (2). Malignancies containing TP53 mutations may be found in the Catalogue Of Somatic Mutations In Cancer (COSMIC) (<http://www.sanger.ac.uk/genetics/CGP/cosmic/>) and in the International Agency for Research on Cancer (IARC) TP53 Database (<http://www-p53.iarc.fr/>). The prevalence of TP53 mutations ranges from 5-50%, depending on the tumor type. Several hematologic malignancies where TP53 mutations have been associated with adverse prognoses are chronic lymphocytic leukemia (3), B-cell acute lymphoblastic leukemia (4), myelodysplastic syndrome (5), acute myeloid leukemia (6), and diffuse large B-cell lymphoma in patients treated with R-CHOP (7).

Li-Fraumeni Syndrome (LFS), an autosomal dominant cancer predisposition syndrome, results from germline mutations in the TP53 gene and predisposes individuals to multiple malignancies, including leukemia, soft tissue sarcomas, osteosarcomas, early onset breast cancer, brain tumors, and adrenocortical carcinomas. Germline mutations in the TP53 gene can be identified in greater than 70% of affected patients and ~95% of mutations can be detected by sequencing analysis. Genetic testing can be used to identify relatives at high risk for developing cancer and also for increased surveillance for LFS-related cancers in those identified to carry a mutation. For an individual with an identified TP53 mutation, the risk of developing any invasive cancer is approximately 50% by age 30 and 90% by age 60. For women with LFS, the lifetime risk of cancer is nearly 100% and for men with LFS, the lifetime cancer risk is about 73% (8).

### REASONS FOR REFERRAL:

- Prognostic marker for various hematologic malignancies.
- Diagnosis of patients with suspected LFS, identification of family members at-risk to develop cancers related to LFS, and prenatal diagnosis in families with a known TP53 gene mutation.
- Investigator initiated and pharmaceutical sponsored clinical trials.

### METHOD:

Bi-directional sequence analysis of the entire coding region (exons 2-11) of the TP53 gene and intron/exon boundaries is performed. Single exon sequencing is available in cases with a known mutation.

### LIMITATIONS:

For somatic mutation detection, the assay is expected to detect >99% of variants within TP53 exons 2-11 that are present at an allele proportion of approximately 20% or greater. For germline mutation detection, the assay is expected to detect 95% of LFS mutations within exons 2-11. Mutations in non-coding sequences and deletions/duplications of one or more exons of the TP53 gene will not be detected.

PO Box 2178  
Milwaukee, WI 53201-2178  
Location/Sample Deliveries:  
638 N. 18th St. Milwaukee, WI 53233-2121  
p800-245-3117 | f414-937-6202 | [www.bcw.edu](http://www.bcw.edu)

**REFERENCE INTERVAL:**

Somatic variants are reported as mutation detected or mutation not detected using standard nomenclature.

Germline variants are reported as heterozygous or homozygous and are classified according to the following system:

- I. Sequence variation is previously reported and is a recognized cause of the disorder
- II. Sequence variation is previously unreported and is of the type which is expected to cause the disorder
- III. Sequence variation is previously unreported and is of the type which may or may not be causative of the disorder
- IV. Sequence variation is previously unreported and is probably not causative of disease
- V. Sequence variation is previously reported and is a recognized neutral variant
- VI. Sequence variations that are not known or expected to be causative of disease, but have been found to be associated with a clinical presentation

Known polymorphisms are not reported but are available upon request.

**SPECIMEN REQUIREMENTS:**

3-5 ml EDTA (lavender top) whole blood or 2-5 ml EDTA bone marrow (bone marrow acceptable only for Tumor). Contact the laboratory to discuss requirements for known mutations and prenatal testing.

**SHIPPING REQUIREMENTS:**

Place the room temperature specimen and requisition in plastic bags, seal and insert in a Styrofoam container. Seal the Styrofoam container, place in a sturdy cardboard box and tape securely. Ship the package in compliance with your overnight carrier guidelines. Address package to:

Client Services/Molecular Oncology Laboratory  
BloodCenter of Wisconsin  
638 N. 18th Street  
Milwaukee, WI 53233  
800-245-3117, ext. 6250

**TURNAROUND TIME:** 5-10 days

**CPT CODES:** 81405

**REFERENCES:**

1. Online Mendelian Inheritance in Man, OMIM®. Johns Hopkins University, Baltimore, MD. MIM Number: 191170 (7/25/12): <http://www.omim.org/entry/191170>
2. Olivier M, Taniere P. Somatic mutations in cancer prognosis and prediction: lessons from TP53 and EGFR genes. *Curr Opin Oncol* 2011;23:88-92.
3. Pospisilova S, et al. ERIC recommendations on TP53 mutation analysis in chronic lymphocytic leukemia. *Leukemia* 2012;26:1458-1461.
4. Hof J, et al. Mutations and Deletions of the TP53 Gene Predict Nonresponse to Treatment and Poor Outcome in First Relapse of Childhood Acute Lymphoblastic Leukemia. *J Clin Oncol* 2011;29:3185-93.
5. Bejar R, et al. Clinical Effect of Point Mutations in Myelodysplastic Syndromes. *N Engl J Med* 2011;364:2496-2506.
6. Grossman V, et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. *Blood* 2012;120:2963-2972.
7. Xu-Monett ZY et al. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. *Blood* 2012;120:3986-3996.
8. Schneider K, Garber J. Li-Fraumeni Syndrome. 1999 Jan 19 [Updated 2010 Feb 9]. In: Pagon RA, Bird TD, Dolan CR, et al., editors. *GeneReviews™* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1311/>