

## Bloom's Syndrome via *BLM* Gene Sequencing – Test #717

**Brief Description of Clinical Features:** Bloom's Syndrome (BS; OMIM 210900) was first described in 1954 as a "congenital" skin disorder in "dwarfs" (Bloom *Am J Dis Child* 88:754-758, 1954). While patients were found to have additional clinical features, such as immune deficiencies and a propensity for cancer (German et al. *Science* 148:506-507, 1965; German *Am J Hum Genet* 21:196-227, 1969), sun-sensitive facial lesions, low birth weight and stunted growth remain the most consistent features of Bloom's Syndrome today. Symptoms of BS are related to increased mutability of proliferating somatic cells, particularly epithelial cells and lymphocytes. When grown in culture and viewed microscopically, cells of BS patients exhibit extensive "chromosome breakage", including gaps and breaks, structural rearrangements, and telomeric associations (German and Crippa *Ann Genet* 9:143-154, 1966). Chromosome breakage ultimately leads to excessive somatic recombination and high mutation rates (Groden and German *Hum Genet* 90:360-367, 1992). About one-third of individuals with BS die by the age of 30 due to complications of cancer, or from chronic lung disease as a result of immune deficiency (German *Cancer Genet Cytogenet* 93:100-106, 1997).

**Genetics:** Bloom's syndrome is an autosomal recessive disorder, caused by homozygous or compound heterozygous mutations in the *BLM* gene (German et al. *Hum Mutat* 28:743-753, 2007). More than 60 unique mutations have been identified in *BLM*. Most (60%) are single nucleotide changes leading to nonsense, missense or splicing mutations, while the remaining are small insertions/deletions (35%) or large deletions of multiple exons (5%). The *BLM* gene encodes a DNA helicase of the RecQ family. RecQ proteins are critical for maintaining the efficiency and integrity of DNA replication (Hickson *Nat Rev Cancer* 3:169-178, 2003); they resolve secondary structures ahead of replication forks, limit recombination to identical sequences, and assist in the replication and maintenance of telomeres (Bennett and Keck *Crit Rev Biochem Mol Biol* 39:79-97, 2004). In addition to these cellular functions, the *BLM* protein may also be important for the Mismatch Repair (MMR) pathway through its interaction with the *MLH1* and *MSH6* proteins (Langland et al. *J Biol Chem* 276:30031-30035, 2001; Pedrazzi et al. *Biol Chem* 384:1155-1164, 2003). Indeed, there is some evidence that heterozygous carriers of a *BLM* mutation have an increased risk for colorectal cancer (Gruber et al. *Science* 297:2013, 2002), a disease most commonly associated with heterozygous mutations in the MMR genes *MLH1*, *MSH2* and *MSH6*.

**Description of This Particular Test:** This test involves bidirectional DNA sequencing of all 21 coding exons (2-22) of the *BLM* gene, plus ~50 bp of flanking non-coding DNA on either side of each exon. As indicated, we will also sequence one (Test #100; \$190) or two exons (Test #200; \$340) in family members of patients with known mutations, or to confirm research results.

**Reference Sequences:** Genomic: NC\_000015.9 mRNA: NM\_000057.2 Protein: NP\_000048.1 CCDS 10363.1

**Indications for Test:** Candidates for this test are patients diagnosed with Bloom's Syndrome. This test is specifically designed for heritable germline mutations and is not appropriate for the detection of somatic mutations in tumor tissue.

**Sensitivity of Test:** In a retrospective study (German et al. 2007), 87% of patients diagnosed with Bloom's Syndrome were reported to have two *BLM* mutations. In 6% of the patients, only one mutation was found for this recessive disease, indicating the second mutation was not detectable by DNA sequencing methods.

**Turnaround Time:** Maximum of 40 calendar days, although most tests are completed in 2 - 3 weeks.

**Specimen Requirements:** See page 4 of Requisition Form.

<b>Price:</b>	<b>Sequencing of the <i>BLM</i> Gene:</b>	<b>\$ 1240</b>
<b>CPT Codes:</b>		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x25	83898 \$ 380	Sequencing x25 83904 \$ 580
Separation x1	83894 \$ 80	Interpretation/Report x1 83912 \$ 130

**Accreditation Info.** CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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