

**Paget Disease of Bone (PDB)
 via Sequential *SQSTM1* and *TNFRSF11A* Gene Sequencing (Test #850)**

Brief Description of Clinical Features: Paget disease of bone (PDB, OMIM#602080) is the second most common metabolic bone disorder that affects up to 2% of the population aged >40 years. The disorder is characterized by focal areas of increased and disorganized bone turnover, leading to bone pain, deformity, pathological fracture, neurological complications, and an increased risk of osteosarcoma (Laurin et al. *Am J Hum Genet* 70:1582-1588, 2002). The axial skeleton is preferentially affected. PDB can be both inherited and sporadic, with the inherited form accounts for about one-third of patients with PDB (Michou et al. *Joint Bone Spine* 73:243-248, 2006).

Genetics: The familial form of PDB is inherited in an autosomal dominant manner with ~80% penetrance (Michou et al. *Joint Bone Spine* 73:243-248, 2006). At least 8 loci have been described in familial PDB cases by linkage studies, suggesting extensive genetic heterogeneity; however disease-causing genes within most of these loci have not yet been discovered. The most important gene underlying PDB is *SQSTM1*, which encodes a scaffold protein (Sequestosome 1) in the nuclear factor κB (NFκB) signaling pathway. Mutations in *SQSTM1* have been reported to account for 20–50% of familial cases and 5–20% of sporadic cases (Ralston et al. *The Lancet* 372:155-163, 2008). A minority of PDB cases are caused by mutation in the *TNFRSF11A* gene, which encodes the receptor activator of NFκB (RANK), a protein essential in osteoclast formation.

Description of This Particular Test: This test involves bidirectional sequencing of *SQSTM1* and *TNFRSF11A* genes (all coding exons plus ~50 bp of flanking non-coding DNA on each side). When a likely causative mutation is detected in *SQSTM1*, testing stops at that point. If no mutation or variant of unknown significance is identified in *SQSTM1*, testing will continue with *TNFRSF11A*. We will also sequence any single exon (Test #100, \$190) in any of these genes for family members of patients with known mutations, or to confirm research results. Tests for individual sequencing of these two genes are also available (see Tests #853 and 854).

Reference Sequences:

Gene	Genomic	mRNA	Protein	CCDS
<i>SQSTM1</i>	NC_000005.9	NM_003900.4	NP_003891.1	34317.1
<i>TNFRSF11A</i>	NC_000018.9	NM_003839.2	NP_003830.1	11980.1

Indications for Test: Candidates for this test are patients with features consistent with PDB.

Sensitivity of Test: Mutations in *SQSTM1* have been reported to account for 20–50% of familial cases and 5–20% of sporadic cases with PDB (Ralston et al. 2008). Sensitivity in familial PDB cases that are caused by *TNFRSF11A* mutations is currently unknown.

Turnaround Time: Maximum of 40 calendar days for the first gene and 10 days each for subsequent gene, although most tests are completed much more rapidly.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: \$ 690 - \$1290

CPT Codes							
Test	83890	83891	83898	83904	83894	83912	Totals
<i>SQSTM1</i> only	\$30 (x1)	\$40 (x1)	\$190 (x12)	\$280 (x12)	\$40 (x1)	\$110 (x1)	\$ 690
Complete Panel	\$30 (x1)	\$40 (x1)	\$390 (x23)	\$580 (x23)	\$80 (x1)	\$170 (x1)	\$1290

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

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