

Alagille Syndrome-1 via *JAG1* Gene Sequencing (Test #427)

Brief Description of Clinical Features: Alagille syndrome (ALGS1, OMIM 118450) is characterized clinically by cholestasis, congenital heart defects, ophthalmic findings, vertebral defects, and characteristic facies. Abnormally low numbers of hepatic bile ducts results in chronic cholestasis which can lead to cirrhosis and end-stage liver disease. Hepatic manifestations are variable, however, and some patients present with jaundice but do not progress to more serious disease. Right-sided cardiac defects are found in almost all patients with pulmonic stenosis being the most common single finding (67%; Emerick et al. *Hepatology* 29:822-829, 1999). Posterior embryotoxon is the most common ophthalmic finding affecting approximately 80% of all individuals with Alagille syndrome (Emerick et al. 1999). Butterfly vertebrae, the most frequent skeletal anomaly, have been found in nearly 90% of patients (Sanderson et al. *Pediatr Radiol* 32:114-119, 2002). Other skeletal findings include hemivertebrae and rib anomalies. Typical facial features of Alagille syndrome include deep-set eyes with moderate hypertelorism, a broad forehead, a prominent pointed chin, and a long straight nose with a bulbous tip. Vascular anomalies and intracranial bleeding are recognized as a significance risk for morbidity and mortality in Alagille syndrome (Lykavieris et al. *Pediatrics* 111:167-170, 2004; Kamath et al. *Circulation* 109:1354-1358, 2004).

Genetics: Alagille syndrome is inherited as an autosomal dominant disorder with reduced penetrance. Approximately 30% to 50% of Alagille syndrome patients have an affected parent and approximately 50% to 70% have *de novo* *JAG1* (OMIM 601920) mutations. Somatic mosaicism for *JAG1* mutations has been reported in five of sixty-one cases (Giannakudis et al. *Eur J Hum Genet* 9:209-216, 2001). Haploinsufficiency for *JAG1* results from intragenic mutations (~90%) or a 20p12 microdeletion (~7%) encompassing all of *JAG1* (Warthen et al. *Hum Mut* 27:436-443, 2006; Spinner, Krantz and Kamath, *GeneReviews*, 2010). One study of 53 mutation positive relatives of probands found that 96% had some feature of the condition (Kamath et al. *J Med Genet* 40:891-895, 2003), although a significant number of individuals (47%) had features that were subclinical. Over 300 *JAG1* mutations have been described. Missense and nonsense are the most abundant class of mutation and are distributed throughout the gene.

Description of This Particular Test: Jagged-1, a cell surface protein ligand for the Notch receptor, is coded by exons 1-26 of the *JAG1* gene on chromosome 20p12. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. This test will not detect *JAG1* gene deletions.

Reference Sequences: **Genomic:** NC_000020.10 **mRNA:** NM_000214.2
 Protein: NP_000205.1 **mRNA and Protein:** CCDS 13112.1

Indication for Testing: Individuals with liver, cardiac, skeletal, ophthalmic, and facial findings consistent with Alagille syndrome. Because clinical manifestations exhibit inter- and intra-familial variability, not all mutation proven cases will have a classic presentation.

Sensitivity of test: Clinical sensitivity of the *JAG1* sequencing test has been shown to be high in patients meeting rigorous phenotypic criteria for this disorder. Warthen et al. (2006) identified intragenic *JAG1* point mutations in almost 90% of a cohort of 247 Alagille syndrome patients. Much less common etiologies include a 20p12 microdeletion detectable by FISH (<10%; Spinner, Krantz and Kamath, 2010) and *NOTCH2* gene mutations detectable by sequence analysis (<1%; McDaniell et al. *Am J Hum Genet* 79:169-173, 2006). Limited sensitivity for detecting *JAG1* mutations among individuals not meeting rigorous phenotypic criteria may be a consequence of a significant rate of mosaicism (Giannakudis et al. 2001).

Turnaround Time: Maximum of 40 days although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Price: Sequencing of <i>JAG1</i> Gene	Exons 1-26	\$ 1090		
CPT Codes:				
Sample Ascertainment	83890 \$ 30	DNA Isolation	83891 \$ 40	
Amplification x22	83898 \$ 330	Sequencing x22	83904 \$ 510	
Separation	83894 \$ 70	Interpretation/Report	83912 \$ 110	

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

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