



Disease Information

Pulmonary arterial hypertension (PAH) is caused by progressive narrowing of pulmonary arteries. This leads to increased pressure in the right side of the heart with symptoms including shortness of breath, chest pain, fatigue, palpitation, edema, and/or fainting. PAH may be associated with an underlying disease or environmental exposures, or may be otherwise classified as familial (with two or more affected relatives) or idiopathic (cause unknown and with negative family history).

Mutations in the *BMPR2* gene are detected in approximately 70% of familial and 11-40% of idiopathic PAH.^{1,2} Mutations are dominantly-inherited, and penetrance is reduced with only approximately 20% of mutation carriers manifesting symptoms of PAH.^{1,2} Correlation of genotype with phenotype has not been found, as onset can vary by several decades within the same family and between unrelated individuals with the same mutation. Genetic anticipation, the increasingly earlier age of onset in subsequent generations, is found in some PAH families.

According to the American College of Chest Physicians' Clinical Practice Guideline, genetic testing and genetic counseling should be offered to relatives of patients with familial PAH, and idiopathic PAH patients should be informed of the availability of testing and counseling for their relatives.³

Testing Benefits & Indications

Genetic testing is available to symptomatic patients and unaffected, at-risk relatives of patients according to the following guidelines.

Diagnostic testing for patients with known or suspected PAH:

In patients positive for a described mutation, the cause of PAH is confirmed and appropriate surveillance may begin or continue for siblings and offspring. Pre- and post-test genetic counseling is recommended. The patient's signature on the PAH Diagnostic Test Consent Form is required.

Carrier testing for at-risk relatives of PAH patients:

As mutations causing approximately 30% of familial PAH are as yet undiscovered, testing for asymptomatic, at-risk relatives is limited to analysis for a disease-causing mutation that has been detected in the affected relative(s) through prior testing. Please call an Ambry Genetics counselor for assistance in arranging family member or carrier testing. Pretest genetic counseling by a genetics professional or the patient's physician is required, as are signatures of this professional and the patient on the PAH Carrier Test Consent Form.

Test Description

The Ambry Test: PAH AMPLIFIED includes concurrent full gene sequence analysis and gross deletion/duplication analysis of the *BMPR2* gene. PCR-based double-stranded automated sequencing is performed in the sense and antisense directions for exons 1-13, the site of a known promoter mutation c.1-946_947GC>TA, at least 20 bases into the 5' ends of all introns, and at least 20 bases into the 3' ends of all introns except 6 and 10. Analysis for gross deletions or duplications of any exon is performed by MLPA®.

The Ambry Test: PAH Del/Dup analyzes only for gross deletions and duplications of the *BMPR2* gene, which account for 5-20% of cases,^{4,5} and is for patients who have tested negative in previous gene sequencing.

Specific mutation analysis for individual *BMPR2* mutations known to be in the family is also available.

Mutation Detection Rate

Approximately 99% of *BMPR2* mutations are detectable by this test.

Turn-Around-Time

PAH AMPLIFIED	14 – 28 days
PAH Del/Dup	7 – 14 days
Specific mutation analysis	10 – 14 days

Specimen Requirements

BLOOD: Collect 3-5 cc from adult or 2 cc minimum from child into EDTA purple-top tube (first choice) or ACD yellow-top tube (second choice). Store at room temperature or refrigerate. Ship at room temperature.

BLOOD SPOT: Minimum of one complete spot approximately 0.5 inch in diameter on S&S 903 collection paper or similar. Store in a clean plastic bag at room temperature. Ship at room temperature.

SALIVA: Collect 2 ml into Oragene™ DNA Self-Collection container. Store and ship at room temperature.

DNA: Send 20 µg in TE at 50-100 ng/µl. Store frozen and ship on ice or dry ice.

PRENATAL: Prenatal testing is available. Please call an Ambry Genetic Counselor to discuss your case.

A signed PAH Diagnostic Test Consent Form or PAH Carrier Test Consent Form is required for testing.

CPT Codes

PAH AMPLIFIED	83891, 83894, 83898, 83900, 83901, 83904, 83909, 83912
PAH Del/Dup	83891, 83894, 83900, 83901, 83909, 83912
Specific mutation analysis	83891, 83894, 83898, 83904, 83909, 83912

References

¹Sztrymf B et al. *Respiration*. 2007;74:123-132.

²Austin ED and Loyd JE. *Clin Chest Med*. 2007;28:43-57.

³McGoon M et al. *Chest*. 2004;126:14-34.

⁴Aldred MA et al. *Hum Mutation*. 2006;27:212-213.

⁵Cogan JD et al. *Am J Respir Crit Care Med*.174;5:590-598