Pyruvate Kinase (PK) Testing – Information for Clinicians

Overview

Pyruvate kinase (PK) deficiency is a genetic disorder caused by mutations in the *PKLR* gene. PK is a key regulatory enzyme of glycolysis. PK deficiency is characterized by low levels of the pyruvate kinase enzyme in red blood cells (RBCs) leading to ATP depletion and increased 2,3-diphosphoglycerate content. Clinically PK deficient patients range from mild chronic hemolysis to severe neonatal jaundice and hydrops at birth. Diagnosis of PK deficiency may include direct enzyme assays and DNA sequencing. The current treatment options for PK deficiency are limited, with the most common being blood transfusion. The prevalence of PK deficiency is estimated at approximately 1 per 20,000 individuals.

Indications for Ordering

- Determine etiology, elicit inheritance pattern, and add recurrence risk in individuals with unexplained hemolytic anemia or a family history of unexplained hemolytic anemia. Symptoms for PK deficiency include a variety of clinical presentation such as, anemia, fatigue, gallstones, hyperbilirubinemia/jaundice, pallor, scleral icterus, and/or splenomegaly.

- The PK assay is the preferred initial test to screen for PK deficiency. The Hereditary Hemolytic Anemia Sequencing (HHA SEQ) assay is used to confirm etiology of hemolytic anemia in individuals with hemolysis or a family history of hemolytic anemia. This assay includes *PKLR* gene responsible for PK deficiency.

- If a recent hemolytic episode has occurred, wait for 30 days before sampling so that both young and old erythrocytes are tested. PK activity is generally greater in reticulocytes than in mature red blood cells; this may explain the false negative enzyme test with hemolytic anemia.

- It is recommended to wait for at least 2, and preferably 3 months, after a transfusion before sampling, in order to minimize the risk of false negative enzyme results due to the contribution of PK activity in healthy donor cells.

Test Methodology

PK: Provides a quantitative measurement of pyruvate kinase activity in RBCs and is performed on an automated clinical chemistry analyzer. For more information please see ARUP test code 0080290: Pyruvate Kinase http://ltd.aruplab.com/Tests/Pub/0080290

HHA SEQ: Involves targeted capture of all coding regions and intron/exon boundaries for 28 genes, including PKLR, involved in genetic forms of hemolytic anemia followed by massively parallel sequencing. For more information please see ARUP test code 2012052: Hereditary Hemolytic Anemia Sequencing, 28 genes http://ltd.aruplab.com/Tests/Pub/2012052

Specimen Requirements

The specimen for PK enzyme and HHA Seq testing is refrigerated EDTA whole blood. Collect ***two*** lavender (EDTA) tubes. Transport one tube with a ***minimum* of 2 mL whole blood *AND*** one tube with a ***minimum* of 2 mL whole blood.** Ship the two whole blood samples and completed test request form on refrigerated gel packs via FedEx to ARUP.

- *Care should be taken to not ship cells directly on cool packs. Lysis can occur if RBCs become frozen.*

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Result Interpretation

The PK assay and HHA Seq Assay will be performed on all samples.

HHA SEQ Results

As the HHA SEQ analyzes 28 genes involved in genetic forms of hemolytic anemia, the results of the test will depend on the type of underlying condition and gene involved. This means that a sample from a patient with a suspected diagnosis of Pyruvate kinase deficiency may reveal the diagnosis of a different form of genetically determined hemolytic anemia.

Positive:	Indicates one or more pathogenic variants detected
Negative:	No pathogenic variants associated with an HHA disorder were identified, however it does *NOT* exclude a diagnosis of HHA
Inconclusive:	Variants of unknown clinical significance were identified

Compliance Statements

*Compliance Statement (PK): Analyte Specific Reagent. This test was developed and its performance characteristics determined by ARUP Laboratories. The U. S. Food and Drug Administration has not approved or cleared this test; however, the FDA has determined that such clearance or approval is not necessary.

*Compliance Statement (HHA SEQ): This test was developed and its performance characteristics determined by ARUP Laboratories. The U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions. Counseling and informed consent are recommended for genetic testing. Consent forms are available online. (https://www.aruplab.com/genetics/resources/consent)

References

- Bolton-Maggs PH, Langer JC, et al. Guidelines for the diagnosis and management of hereditary spherocytosis – 2011 update. Br J Haematol. 2012;156(1):37-49
- Gallagher PG. Abnormalities of the erythrocyte membrane. Pediatr Clin North Am. 2013;60(6):1349-1362
- Koralkova P, van Solinge WW, et al. Rare hereditary red blood cell enzymopathies associated with hemolytic anemia- pathophysiology, clinical aspects, and laboratory diagnosis. Int Jnl Lab Hem. 2014;36:388-397