Test Definition: BPGMM

BPGM Full Gene Sequencing

Overview

Useful For

Diagnosis of 2,3-bisphosphoglycerate mutase deficiency in individuals with lifelong, unexplained erythrocytosis

Identifying genetic variant carriers in family members of an affected individual for the purposes of preconception genetic counseling

This test is **not intended** for prenatal diagnosis.

Genetics Test Information

The *BPGM* gene encodes the enzyme 2,3-bisphosphoglycerate mutase (BPGM) that catalyzes the conversion of 1,3-bisphosphoglycerate to 2,3-bisphosphoglycerate (2,3-BPG), also known as 2,3-diphosphoglycerate (2,3-DPG), through the Luebering-Rapoport pathway. 2,3-BPG is a small molecule generated from glycolysis and is present in large amounts in red blood cells. It functions to stabilize the hemoglobin molecule and facilitates oxygen unloading at tissue sites. Therefore, 2,3-BPG concentrations affect the oxygen affinity of hemoglobin. Variations in this gene that result in a deficiency of 2,3-BPG can cause hereditary erythrocytosis.

This test can detect variants in *BPGM* that are associated with unexplained lifelong erythrocytosis due to bisphosphoglycerate mutase deficiency.

Testing Algorithm

This evaluation is recommended for patients presenting with lifelong elevation in hemoglobin or hematocrit, usually with a positive family history of similar symptoms. Reported cases of 2,3- bisphosphoglycerate (BPG) deficiency have been associated with decreased p50 values (left-shifted oxygen-dissociation curve). Due to the rarity of this disorder, other more common causes of erythrocytosis should be excluded prior to ordering; see Erythrocytosis Evaluation Testing Algorithm in Special Instructions.

Polycythemia vera and chronic myeloproliferative neoplasm should be excluded prior to testing as they are more common causes of elevated hemoglobin values. A *JAK2* V617F or *JAK2* exon 12 variant should not be present. Patient serum erythropoietin levels are typically normal or elevated and oxygen dissociation p50 values decreased in test candidates. For a reflexive evaluation including p50 testing, hemoglobin electrophoresis, and variant analysis of genes associated with hereditary erythrocytosis, order REVE1 / Erythrocytosis Evaluation, Whole Blood.

Special Instructions

- Informed Consent for Genetic Testing
- Erythrocytosis Patient Information
- Erythrocytosis Evaluation Testing Algorithm
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR)/Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

This test detects variants identifiable by Sanger sequencing in the *BPGM* gene only. For a complete evaluation in an algorithmic fashion, order REVE1 / Erythrocytosis Evaluation, Whole Blood.

This test does not provide a serum erythropoietin (EPO) level. If EPO testing is desired, order EPO / Erythropoietin, Serum.

Specimen Required

Submit only 1 of the following specimens:

Patient Preparation: Bone marrow transplants preclude accurate germline and genetic variant analysis. Please inform the laboratory if this patient has undergone bone marrow transplantation. On rare occasions transfusion of blood products can preclude accurate genetic variant analysis and results should be interpreted with caution if performed after recent transfusion (within 4 months).

Specimen Type: Peripheral blood

Container/Tube:

Preferred: Lavender top (EDTA)

Acceptable: Yellow top (ACD), green top (sodium heparin)

Specimen Volume: 4 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in the original tube.

Stability Information: Ambient 14 days (preferred)/Refrigerate 30 days

Specimen Type: Extracted DNA from whole blood

Container/Tube: 1.5- to 2-mL tube

Specimen Volume: Entire specimen

Collection Instructions:

1. Label specimen as extracted DNA and source of specimen

2. Provide volume and concentration of the DNA

Specimen Stability Information: Frozen (preferred)/Refrigerate/Ambient

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Erythrocytosis Patient Information (T694) in Special Instructions

3. If not ordering electronically, complete, print, and send a Benign Hematology Test Request Form (T755) with the specimen.

Reject Due To

Gross hemolysis	Reject
Bone marrow Paraffin-embedded tissue Frozen tissue Paraffin-embedded bone marrow aspirate clot Methanol-acetic acid (MAA)-fixed pellets Moderately to severely clotted	Reject

Specimen Minimum Volume

Blood: 1 mL

Extracted DNA: 50 mcL at 50 ng/mcL concentration

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies (preferred)		

Clinical & Interpretive

Clinical Information

Erythrocytosis (ie, increased red blood cell mass and elevated hemoglobin and hematocrit) may be primary, due to an intrinsic defect of bone marrow stem cells as in polycythemia vera (PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanism may be suspected.

Unlike PV, hereditary erythrocytosis is not associated with the risk of clonal evolution and most commonly presents as isolated erythrocytosis that has been present since childhood. Hereditary erythrocytosis may be caused by alterations in one of several genes and inherited in either an autosomal dominant or autosomal recessive manner.

Genetic variants causing hereditary erythrocytosis have been found in genes coding for alpha and beta hemoglobins, hemoglobin stabilization proteins (eg, 2,3-bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF, prolyl hydroxylase domain: PHD, and von Hippel Lindau: VHL), see table. High-oxygen-affinity hemoglobin variants and *BPGM* abnormalities result in a decreased p50 result, whereas those affecting *EPOR*, *HIF, PHD*, and *VHL* have normal p50 results. The true prevalence of variants causing hereditary erythrocytosis is unknown; however, very few cases of 2,3-BPG deficiency-associated hereditary erythrocytosis have been identified and this disorder is thought to be rare.

Erythrocytosis Testing

Gene	Inheritance	Serum Epo	p50
JAK2 V617F	Acquired	Decreased	Normal
JAK2 exon 12	Acquired	Decreased	Normal
EPOR	Dominant	Decreased	Normal
PHD2/*EGLN1*	Dominant	Normal	Normal to mildly decreased
BPGM	Recessive	Normal	Decreased

Beta globin	Dominant	Normal to increased	Decreased
Alpha globin	Dominant	Normal to increased	Decreased
HIF2A/*EPAS1*	Dominant	Normal to increased	Normal
VHL	Recessive	Normal to increased	Normal

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any variations in the gene. If positive, the alteration will be correlated with clinical significance, if known.

Cautions

This test does not detect large deletions and duplications in *BPGM*.

Polycythemia vera and acquired causes of erythrocytosis should be excluded before ordering this test. The p50 value should be decreased.

Certain genetic alterations have no clinical manifestations and, in essence, are clinically benign. Correlation with all relevant clinical information is necessary to provide appropriate patient care.

Clinical Reference

1. Petousi N, Copley RR, Lappin TR, et al: Erythrocytosis associated with a novel missense mutation in the BPGM gene. Haematologica. 2014 Oct;99:e201-e204

2. Hoyer JD, Allen SL, Beutler E, et al: Erythrocytosis due to bisphosphoglycerate mutase deficiency with concurrent glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Am J Hematol. 2004;75(4):205-208

3. Rosa R, Prehu MO, Beuzard Y, Rosa J: The first case of a complete deficiency of diphosphoglycerate mutase in human erythrocytes. J Clin Invest. 1978;62(5):907-915

Performance

Method Description

DNA is extracted from whole peripheral blood and amplified in 4 separate polymerase chain reactions (PCR) to cover *BPGM* exons 1 through 4. PCR products are then sequenced by the Sanger sequencing method and analyzed with

sequencing software. Patient sequence results are compared with the genomic reference sequences and the single-nucleotide variants known to occur in the genes. If a variant is detected, the messenger RNA reference sequence will be used to determine the amino acid number and resulting amino acid change if there is one.(Lemarchandel V, Joulin V: Compound heterozygosity in a complete erythrocyte bisphosphoglycerate mutase deficiency. Blood. 1992 Nov;80[10]:2643-2649; McMullin MF: Congenital erythrocytosis. IJLH 2016;38[Suppl. 1]:59-65)

PDF Report
No

Specimen Retention Time
DNA 3 months

Performing Laboratory Location
Rochester

Fees & Codes

Test Classification
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
81479-Unlisted Molecular Pathology procedure

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
BPGMM	BPGM Full Gene Sequencing	94190-6

Result ID	Reporting Name	LOINC®
37111	BPGM Gene Sequencing Result	No LOINC Needed
37112	BPGM Interpretation	69047-9