Overview

Useful For

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

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

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. Mutations in this gene that result in a deficiency of 2,3-BPG can cause hereditary erythrocytosis.

This test can detect mutations 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-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 mutation 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 mutation analysis of genes associated with hereditary erythrocytosis, order REVE / Erythrocytosis Evaluation.

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) Amplification/Sanger Sequence Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies
Advise Information
This test detects mutations identifiable by Sanger sequencing in the BPGM gene only. For a complete evaluation in an algorithmic fashion, order REVE/ Erythrocytosis Evaluation.

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

Shipping Instructions
Specimens must arrive within 7 days (168 hours) of collection.

Specimen Required
Submit only 1 of the following specimens:

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

Specimen Type: Peripheral blood

Collection Container/Tube:
Preferred: EDTA (lavender top)
Acceptable: ACD (yellow top), Heparin (green top)

Specimen Volume: 4 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in the original tube.

Specimen Stability: Ambient (preferred)/Refrigerate

Specimen Type: Extracted DNA from whole blood

Container/Tube: 1.5- to 2-mL tube

Specimen Volume: Entire specimen

Collection Instructions: Label specimen as extracted DNA from blood and provide indication of volume and concentration of the DNA

Specimen Stability: 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.

### Specimen Minimum Volume

1 mL

### Reject Due To

<table>
<thead>
<tr>
<th>Gross hemolysis</th>
<th>Reject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>Paraffin-embedded tissue</td>
</tr>
<tr>
<td>Frozen tissue</td>
<td></td>
</tr>
<tr>
<td>Paraffin-embedded bone</td>
<td>marrow aspirate clot</td>
</tr>
<tr>
<td>MAA-fixed pellets</td>
<td>Moderately to severely clotted</td>
</tr>
</tbody>
</table>

### Specimen Stability Information

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
<th>Special Container</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varies</td>
<td>Varies</td>
<td>7 days</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical and Interpretive

### Clinical Information

Erythrocytosis (ie, increased RBC 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 mutations in one of several genes and inherited in either an autosomal dominant or autosomal recessive manner.

Genetic mutations 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 mutations 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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Inheritance</th>
<th>Serum Epo</th>
<th>p50</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2 V617F</td>
<td>Acquired</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>JAK2 exon 12</td>
<td>Acquired</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>EPOR</td>
<td>Dominant</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>PHD2/EGLN1</td>
<td>Dominant</td>
<td>Normal</td>
<td>Normal to mildly decreased</td>
</tr>
<tr>
<td>BPGM</td>
<td>Recessive</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Beta Globin</td>
<td>Dominant</td>
<td>Normal to increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Alpha Globin</td>
<td>Dominant</td>
<td>Normal to increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>HIF2A/EPAS1</td>
<td>Dominant</td>
<td>Normal to increased</td>
<td>Normal</td>
</tr>
<tr>
<td>VHL</td>
<td>Recessive</td>
<td>Normal to increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

### 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 mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

### Cautions

This test does not detect large deletions and duplications in 2,3-bisphosphoglycerate mutase (BPGM).

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

This test is not intended for prenatal diagnosis.

Certain mutations 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


Performance

Method Description
DNA is extracted from whole peripheral blood and amplified in 4 separate PCR reactions 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 polymorphisms known to occur in the genes. If a mutation 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)

PDF Report
No

Day(s) and Time(s) Test Performed
Monday through Friday

Analytic Time
10 days

Maximum Laboratory Time
25 days

Specimen Retention Time
DNA 3 months

Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

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 U.S. Food and Drug Administration.

CPT Code Information
81479-Unlisted Molecular Pathology procedure

LOINC® Information

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Test Order Name</th>
<th>Order LOINC Value</th>
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</thead>
<tbody>
<tr>
<td>BPGMM</td>
<td>BPGM Full Gene Sequencing</td>
<td>In Process</td>
</tr>
</tbody>
</table>
## Test Definition: BPGMM

BPGM Full Gene Sequencing

<table>
<thead>
<tr>
<th>Result ID</th>
<th>Test Result Name</th>
<th>Result LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>37111</td>
<td>BPGM Gene Sequencing Result</td>
<td>No LOINC Needed</td>
</tr>
<tr>
<td>37112</td>
<td>BPGM Interpretation</td>
<td>69047-9</td>
</tr>
</tbody>
</table>