Overview

Useful For
Definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

This test is not intended for prenatal diagnosis.

Genetics Test Information
This test is a third-order test and should be ordered when the patient meets the following criteria: diagnosis of erythrocytosis, JAK2 V617F is negative, and p50 values are normal.

Profile Information

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINT</td>
<td>Molecular Interpretation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>EPOR</td>
<td>EPOR Gene, Mutation Analysis, B</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>HIF2A</td>
<td>HIF2A Gene, Mutation Analysis, B</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PHD2</td>
<td>PHD2 Gene, Mutation Analysis, B</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Additional Tests

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Available Separately</th>
<th>Always Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPGMM</td>
<td>BPGM Full Gene Sequencing</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>VHLE</td>
<td>VHL Gene Erythrocytosis Mutations</td>
<td>No, (Order VHLZ)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Testing Algorithm
This evaluation is recommended for patients presenting with lifelong erythrocytosis, usually with a positive family history of similar symptoms. Polycythemia vera should be excluded prior to testing as it is much more common than hereditary erythrocytosis and can be present even in young patients. A JAK2 V617F or JAK2 exon 12 variant should not be present. Additionally, p50 testing should be performed and a normal result confirmed before ordering this test.

Additional testing for BPGM full gene sequencing and VHL gene erythrocytosis variant analysis will always be performed at an additional charge.

See Erythrocytosis Evaluation Testing Algorithm in Special Instructions.

Special Instructions
- Informed Consent for Genetic Testing
Method Name
Polymerase Chain Reaction (PCR) Amplification/Sanger Sequence Analysis

NY State Available
Yes

Specimen

Specimen Type
Whole blood

Advisory Information
This is a third-order test for specific variants. For a complete evaluation including p50 testing, hemoglobin electrophoresis testing, and hereditary erythrocytosis variant analysis in an algorithmic fashion, order REVE / Erythrocytosis Evaluation, Whole Blood.

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

Specimen Required

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions: Send specimen in original tube.

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
0.5 mL

Reject Due To

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross hemolysis</td>
<td>Reject</td>
</tr>
<tr>
<td>Gross lipemia</td>
<td>Reject</td>
</tr>
<tr>
<td>Gross icterus</td>
<td>Reject</td>
</tr>
</tbody>
</table>
Test Definition: HEMP
Hereditary Erythrocytosis Mut, B

| Moderately to severely clotted | Reject |

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>Whole blood</td>
<td>Refrigerated (preferred)</td>
<td>30 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ambient</td>
<td>14 days</td>
<td></td>
</tr>
</tbody>
</table>

Clinical and Interpretive

Clinical Information

Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, 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 (due to smoking), 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 mechanisms may be suspected.

Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by variations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new variants to arise in an individual.

The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (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 hereditary erythrocytosis-causing variants is unknown. The hemoglobin genes, HBA1/HBA2 and HBB are not assayed in this profile.

Genes Associated with Hereditary Erythrocytosis

<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 level</td>
<td>Normal</td>
</tr>
<tr>
<td>BPGM</td>
<td>Recessive</td>
<td>Normal level</td>
<td>Decreased</td>
</tr>
<tr>
<td>Beta Globin</td>
<td>Dominant</td>
<td>Normal level to increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Alpha Globin</td>
<td>Dominant</td>
<td>Normal level to increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including \( EPO, VEGF, \) and \( GLUT1 \). HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the \( HIF2A \) (\( EPAS1 \)) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the \( PHD2 \) (\( EGLN1 \)) gene. Variations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of variants, in \( PHD2/EGLN1 \) and \( HIF2A/EPAS1 \), has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas.

Truncating variants in the \( EPOR \) gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known variants have been localized to exon 8 and are heterozygous truncating variants. \( EPOR \) variants are associated with decreased EPO levels and normal p50 values (see 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 variations in the gene. If positive, the variant will be correlated with clinical significance, if known.

### Cautions
Polycythemia vera and acquired causes of erythrocytosis should be excluded before ordering this evaluation. The p50 value should be normal.

This test will not detect somatic or gonadal mosaicism.

Certain sequence 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


**Performance**

**Method Description**


**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>
</tr>
</thead>
<tbody>
<tr>
<td>HEMP</td>
<td>Hereditary Erythrocytosis Mut, B</td>
<td>In Process</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result ID</th>
<th>Test Result Name</th>
<th>Result LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>34645</td>
<td>EPOR Gene Sequencing Result</td>
<td>82939-0</td>
</tr>
<tr>
<td>34646</td>
<td>PHD2 Gene Sequencing Result</td>
<td>82939-0</td>
</tr>
<tr>
<td>34647</td>
<td>HIF2A Gene Sequencing Result</td>
<td>82939-0</td>
</tr>
<tr>
<td>34648</td>
<td>Molecular Interpretation</td>
<td>69047-9</td>
</tr>
<tr>
<td>35000</td>
<td>Reviewed By</td>
<td>18771-6</td>
</tr>
</tbody>
</table>