Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare hemolytic disorder caused by nonmalignant clonal expansion of one or more stem cell lines due to an acquired mutation in the *PIGA* gene. PNH is associated with intravascular hemolysis, thrombotic complications, and bone marrow failure.  

### TYPICAL TESTING STRATEGY

- **Initial testing includes:**
  - Complete blood count with peripheral smear
  - Reticulocyte count
  - Direct Coombs test
  - Serum lactate dehydrogenase
  - Indirect bilirubin
  - Serum haptoglobin
- **Diagnostic testing (if suspicion exists based on primary tests) should include flow cytometry of both white blood cells (WBCs) and red blood cells (RBCs)**
- **Flow cytometry testing of WBCs and/or RBCs may be used in therapeutic monitoring**
  - Ham and sugar water tests are no longer used; do not order

### Incidence

1.3/million

### Symptoms

- Hemolysis
  - Symptoms include dysphagia, lethargy, renal failure, anemia, hemoglobinuria, male impotence, pulmonary hypertension
- Thrombophilia
  - Potentially life-threatening
  - Thromboses located at unusual sites (eg, hepatic portal)
- Bone marrow (BM) failure
  - May present as severe aplastic anemia

### Physiology

- PNH is caused by a somatic mutation of *PIGA* gene which results in deficiency or absence of glycosylphosphatidylinositol (GPI)-anchored cell membrane proteins on progeny of affected stem cells
  - Lack of CD55 and CD59 causes RBC sensitivity to complement lysis
  - Pathophysiology of thrombophilia and bone marrow failure in PNH is unknown
- Percentage of RBCs or WBCs that entirely or partially lack GPI-linked antigens is referred to as PNH clone size
  - **Type I:** normal levels of CD59
  - **Type II:** reduced levels of CD59
  - **Type III:** absent levels of CD59

### Related Tests

- **Paroxysmal Nocturnal Hemoglobinuria, High Sensitivity, RBC and WBC 2005006**
  - Method: Quantitative Flow Cytometry
  - Preferred test for initial diagnosis of PNH and quantification of PNH clones
  - Includes high-sensitivity WBC and RBC analysis

- **Paroxysmal Nocturnal Hemoglobinuria, High Sensitivity, WBC 2005003**
  - Method: Quantitative Flow Cytometry
  - Quantify or monitor PNH clone

### Indications for Ordering

Diagnose PNH in patients with

- Unexplained hemoglobinuria
- Coombs-negative hemolytic anemia
- Unusual thrombotic sites (eg, Budd-Chiari, cerebral)
- Thrombosis combined with intravascular hemolysis or cytopenias
- Aplastic or hypoplastic anemia

Monitor individuals with confirmed PNH

- **Incidence**
  - 1.3/million

- **Symptoms**
  - Hemolysis
  - Symptoms include dysphagia, lethargy, renal failure, anemia, hemoglobinuria, male impotence, pulmonary hypertension
  - Thrombophilia
  - Potentially life-threatening
    - Thromboses located at unusual sites (eg, hepatic portal)
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- **Tests to Consider**
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Analytical Sensitivity

Limits of detection:
- RBCs: 0.005%
- Polymorphonuclear neutrophils (PMNs or granulocytes): 0.005%
- Monocytes: 0.020%

Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Cells Detected</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>Positive</td>
<td>PNH cells: ≥1% in RBCs and WBCs</td>
<td>Indicates PNH</td>
</tr>
<tr>
<td></td>
<td>RBC PNH cells: ≥0.005% to &lt;1%</td>
<td>Indicates subclinical PNH</td>
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<td></td>
<td>WBC (PMN) PNH cells: ≥0.005% to &lt;1%</td>
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<tr>
<td></td>
<td>Monocyte PNH cells: ≥0.020% to &lt;1%</td>
<td>Often associated with symptoms of bone marrow failure</td>
</tr>
<tr>
<td>Negative</td>
<td>PNH cells: not detected</td>
<td>Reduces, but does not eliminate the probability of PNH</td>
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Limitations
- Conditions that may compromise accuracy include significant neutropenia, gross hemolysis, and specimens that lack expression of CD15, CD64, or glycophorin A
- Recent RBC transfusions may decrease percentage of PNH cells measured in RBCs

REFERENCES


RELATED INFORMATION

Paroxysmal Nocturnal Hemoglobinuria - PNH