Paroxysmal Nocturnal Hemoglobinuria (PNH):

Risk, Severity, Signs, Symptoms, and When to Test

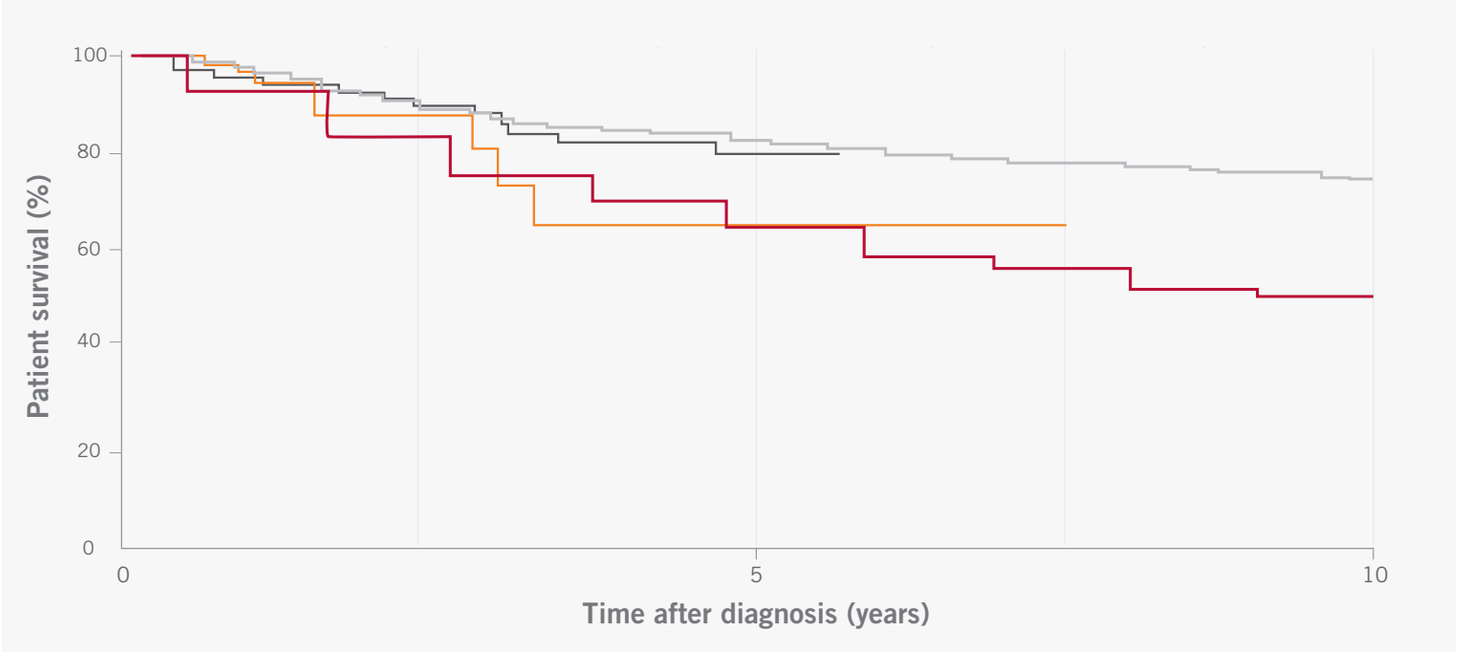
PNH is a chronic, devastating, and potentially life-threatening disease characterized by uncontrolled terminal complement–mediated attack on red and white blood cells and platelets that can lead to severe consequences of thrombosis, organ damage, and early mortality.[1]

Diagnostic delay can be a source of distress and affects patients' emotional well-being.[2]

PNH is likely one of the most vicious acquired thrombophilic states known in medicine[3-5]

- Up to **35%** of PNH patients die within 6 years despite historical supportive care.[6,7,a]

Historical survival rates in patients with PNH[6-9,b]



- Peffault de Latour, et al. *Blood*. 2008. 10-year mortality (6.8 years median follow-up time) in patients diagnosed with PNH between 1950 and 2005 across France (N=454)[8,c]
- Loschi, et al. *Am J Hematol*. 2016. 6-year mortality in historical control patients diagnosed with PNH between 1985 and 2005 in France (N=100)[6]
- Kelly, et al. *Blood*. 2011. Mortality in patients diagnosed with PNH between 1997 and 2004 in Leeds, UK (N=30)[7]
- Hillmen, et al. *N Engl J Med*. 1995. 10-year mortality in patients diagnosed with PNH between 1940 and 1970 in London, UK (N=80)[9,d]

[a]Supportive care included blood transfusion, anticoagulation, immunosuppressive therapy, and bone marrow transplantation.[6,7] [b]These data reflect observations from multiple studies conducted under different conditions and in different patient populations, which may limit generalizability. [c]Patients in the Peffault de Latour 2008 study were followed up to 40 years.[8] [d]Patients in the Hillmen 1995 study were followed up to 25 years.[9]

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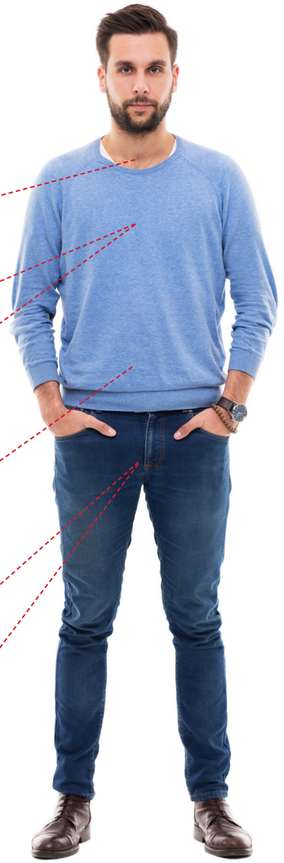
Signs and symptoms of PNH can include a wide range of unpredictable and potentially life-threatening complications[10,11,a]



- **Fatigue** 80%[10]
- **Anemia** 88%-94%[12]
- **Dysphagia** 24%[11]
- **Dyspnea** 64%[10]
- **Chest pain** 33%[10,11]
- **Abdominal pain** 44%[11]
- **Hemoglobinuria** 62%[10]
- **Erectile dysfunction**[b] 38%[11]

Historically, approximately...

16% to 46%
of PNH deaths were due to venous or arterial **thrombosis**[6,8,13]

2% to 18%
of PNH deaths were associated with **renal failure**[12,13,d,f]

47%
of patients suffered from **pulmonary hypertension**[14,g]

Approximately 20% to 35% of patients with PNH die within 6 years of diagnosis despite historical supportive care[7,12,c,h,i]

Terminal complement activation results in intravascular hemolysis, leading to potentially devastating consequences in PNH[15]

[a]The percentages for the signs and symptoms of PNH (with exception of anemia) are from Schrezenmeier 2014 and supplement: PNH Global registry with 856 patients self-reporting symptoms via a baseline questionnaire.[11,12] [b]Male patients only (n=410).[12] [c]Retrospective 6-year survival in historical control patients diagnosed with PNH between 1985 and 2005 in France (N=100). Retrospective thrombosis data presented are also from historical control group (N=44).[7] [d]Retrospective chart review of patients diagnosed with PNH in South Korea (N=301).[13] [e]Retrospective study of patients diagnosed with PNH (N=465) between 1950 and 2005 in France.[6] [f]Retrospective study comparing patients diagnosed with PNH since 1966 from the United States (N=176) to patients with PNH in a database registry in Japan (N=209).[10] [g]Data from patients with PNH enrolled in an international phase 3 randomized, placebo-controlled trial between October 2004 and June 2005 (N=87).[14] [h]Five-year survival in patients diagnosed with PNH between 1997 and 2004 in Leeds, UK (N=30).[8] [i]Supportive care included blood transfusion, anticoagulation, immunosuppressive therapy, corticosteroids, and bone marrow transplantation.[7,8]

PNH is a hemolytic disease caused by an acquired mutation in hematopoietic stem cells and characterized by terminal complement–mediated intravascular hemolysis[16]

In patients with PNH, an acquired mutation in the *PIG-A* gene prevents the production of GPI anchors and results in the lack, or reduced expression, of GPI-anchored complement regulatory proteins, leading to dysregulation of the complement system.[16,17]

Hematopoietic stem cells in bone marrow

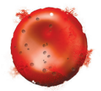
Normal hematopoietic stem cells

Normal red blood cell

GPI-anchored complement regulatory proteins

In healthy red blood cells, GPI-anchored complement regulatory proteins (CD55 and CD59)[a] defend against complement-mediated hemolysis.[16]

Hematopoietic stem cells with acquired mutation in *PIG-A* gene



PNH blood cell

No GPI-anchored complement regulatory proteins

In PNH, an acquired *PIG-A* mutation can lead to the complete or partial absence of GPI-anchored complement regulatory proteins. Red blood cells lacking surface expression of GPI-anchored complement regulatory proteins have increased sensitivity to complement attack. White blood cells and platelets without the GPI-anchored complement regulatory proteins are activated by complement attack.[16]

PNH is an acquired hemolytic disease caused by a genetic mutation in hematopoietic stem cells[16]

- PNH has **multifactorial symptoms** that result in many patients experiencing a lengthy and complex path to diagnosis, with high morbidity and early mortality.[18]
- **24% of all PNH diagnoses can take 5 years or longer, while approximately 60% take longer than 1 year to diagnose.[19]**
- **PNH is characterized by terminal complement–mediated intravascular hemolysis**, which can lead to the devastating and potentially life-threatening consequences of thrombosis, multi-organ failure, and early mortality.[1]
- PNH impacts both **children** and **adults** and is believed to affect males and females in equal numbers.[20,21]
- The **median age** at diagnosis is **during the 30s.[12,22]**
- **A majority of patients (80%) with PNH** report experiencing fatigue, which can result in decreased physical activity and quality of life.[10,23,24]

[a]Complement-inhibiting proteins CD55 (decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis) defend red blood cells against complement-mediated lysis by regulating the formation and stability of the C3 convertase and blocking the assembly of the membrane attack complex, respectively.[5]

Abbreviations: FLAER=fluorescent aerolysin; **GPI**=glycosylphosphatidylinositol; **LDH**=lactate dehydrogenase; ***PIG-A***=phosphatidylinositol glycan complementation class A; **PNH**=paroxysmal nocturnal hemoglobinuria.

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Rapid recognition of the signs and symptoms of PNH and early diagnosis are important to patient management[25,26]

The International Clinical Cytometry Society and International PNH Interest Group recommend testing high-risk patients.[26-28]

Patients who meet the criteria within any of the high-risk groups for PNH should be tested for PNH with high-sensitivity flow cytometry with FLAER on peripheral blood, the standard diagnostic test for PNH.[25,28-30]

Core signs and symptoms of PNH (any of the following)[18,25,28,31,32]

- **Symptoms of anemia** (eg, fatigue, tachycardia, shortness of breath, headache)
- **Thrombosis**
- **Dark-colored urine**
- **Intermittent abdominal pain**
- **Esophageal spasms**
- **Dysphagia**

in association with 1 of the following or if the patient exhibits 1 of the following (in the absence of an above symptom)

High-risk groups associated with PNH[18,25,28,31-33]

- **Bone marrow dysfunction**
- **Unprovoked[a] and unexplained thrombosis**
- **Hemolysis**
  Any of: ↑LDH ↓haptoglobin ↑reticulocyte count ↑bilirubin

C A T C H

- **Unexplained cytopenia[b]**
  - With any of the following:
    - Any subtype[c] with evidence of hemolysis
    - Refractory iron deficiency anemia
    - Nonresponsive to therapy
    - Thrombosis
- **Aplastic anemia**
  - **Myelodysplastic syndrome**
    - With any of the following:
      - Any subtype with evidence of hemolysis
      - Hypoplastic
      - Refractory cytopenia
- **Thrombosis venous or arterial**
  - With any of the following:
    - Evidence of hemolysis
    - Usual and unusual sites[d]
    - Any cytopenia
    - Nonresponsive to anticoagulant
- **Coombs-negative hemolytic anemia**
- **Hemoglobinuria or hemosiderinuria**

With or without signs of: Renal dysfunction

Test for PNH with high-sensitivity flow cytometry with FLAER on peripheral blood, the gold-standard diagnostic test for PNH[18,25,30,e]

This algorithm is intended as educational information for healthcare providers. It does not replace a healthcare provider's professional judgment or clinical diagnosis.

Establish a definitive diagnosis via high-sensitivity flow cytometry with FLAER on peripheral blood, the gold-standard diagnostic test for PNH[25,27,30,31,34]

[a]Deep vein thrombosis and/or pulmonary embolism in a patient with no antecedent major clinical risk factor for venous thromboembolism that is not provoked by surgery, trauma, immobilization, hormonal therapy (oral contraceptive or hormone replacement therapy), or active cancer.[18] [b]Unexplained persistent cytopenia in a patient in whom (minimal) diagnostic criteria for myelodysplastic syndrome are not fulfilled.[18] [c]Anemia, neutropenia, or thrombocytopenia.[35] [d]Unusual sites include hepatic veins (Budd-Chiari syndrome), other intra-abdominal veins (portal, splenic, splanchnic), cerebral sinuses, and dermal veins.[25] [e]Detects PNH cells down to a 0.01% clone size.[25]

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