

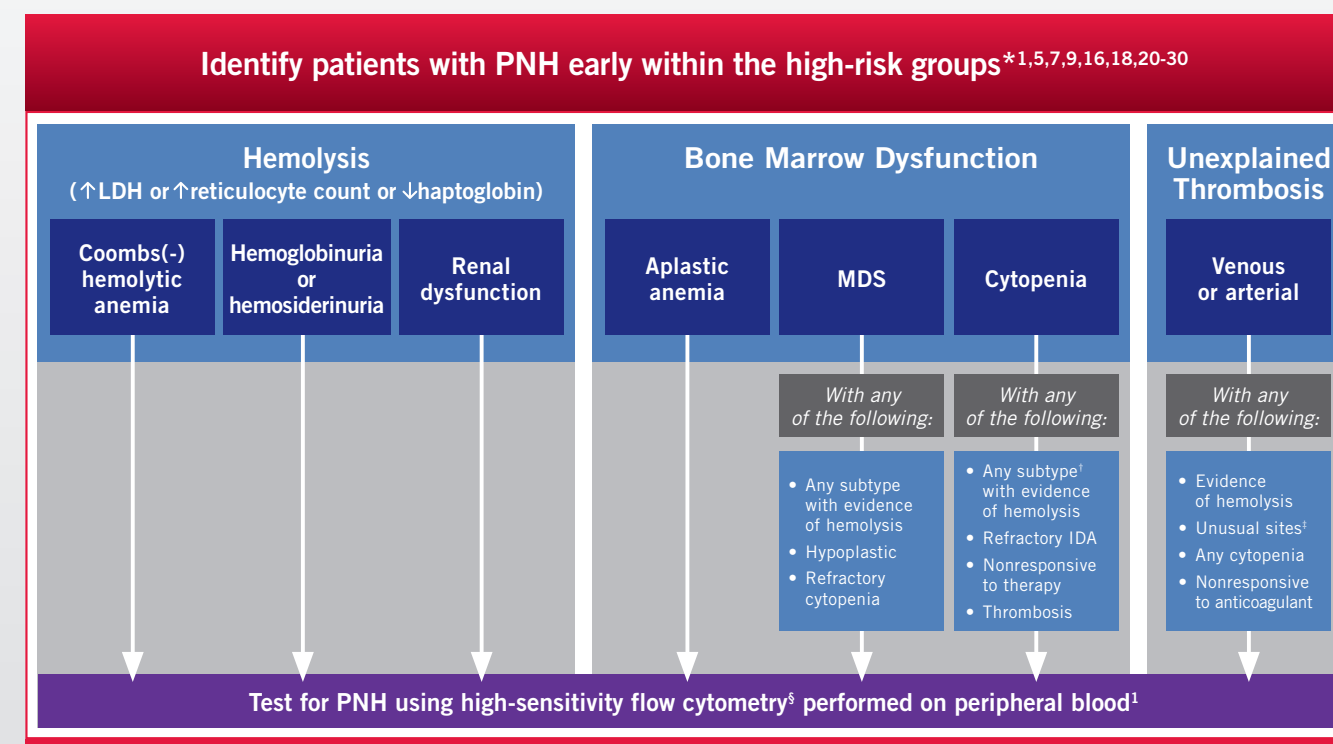
The diverse and common symptomatology of PNH can delay diagnosis^{9,10}

- Diagnosis typically delayed from 1 to more than 10 years¹¹
- Nearly three-fourths of patients with PNH do not present with hemoglobinuria⁹
- Diverse symptomatology of PNH drives the need for a comprehensive clinical assessment and routine diagnostic approach^{8,9,12-14}

Identification of PNH cells has important prognostic and therapeutic implications^{9,15}

- The International Clinical Cytometry Society (ICCS) and International PNH Interest Group (IPIG) recommend continued monitoring of patients at high risk for PNH^{1,9}
- High-sensitivity flow cytometry* (HSFC)—performed on peripheral blood—is the gold standard diagnostic test for PNH¹

Early diagnosis is essential for improved patient management and prognosis^{1,16,17,18,19}



IDA = iron deficiency anemia; MDS = myelodysplastic syndrome.

*The information on this page is intended as educational information for healthcare providers. It does not replace a healthcare professional's judgment or clinical diagnosis.

†Anemia, neutropenia, thrombocytopenia, or pancytopenia.

‡Unusual sites include hepatic veins (Budd-Chiari syndrome), other intra-abdominal veins (portal, splenic, splanchnic), cerebral sinuses, and dermal veins.

§Detects PNH cells down to a 0.01% clone size.

- International Clinical Cytometry Society guidelines (ICCS) and other expert findings suggest that the clinical presentations outlined above increase the likelihood of PNH^{1,5,7,9,16,18,20-30}

References: 1. Borowitz MJ, Craig FE, DiGiuseppe JA, et al. for Clinical Cytometry Society. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry Part B*. 2010;78B:211-230. 2. Richards SJ, Hill A, Hillmen P. Recent advances in the diagnosis, monitoring, and management of patients with paroxysmal nocturnal hemoglobinuria. *Cytometry Part B*. 2007;72B:291-298. 3. Hillmen P, Lewis SM, Bessler M, et al. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 1995;333:1253-1258. 4. Brodsky RA. Advances in the diagnosis and therapy of paroxysmal nocturnal hemoglobinuria. *Blood Rev*. 2008;22:65-74. 5. Rachidi S, Musallam KM, Taher AI. A closer look at paroxysmal nocturnal hemoglobinuria. *Eur J Intern Med*. 2010;21:260-267. 6. Hillmen P, Maus P, Dührsen U, et al. *Blood*. 2007;110:4123-4128. 7. Hillmen P, Elebute M, Kelly R, et al. *Am J Hematol*. 2010;85:253-259. 8. Hill A, Rother RP, Wang X, et al. *Br J Haematol*. 2010;149:414-425. 9. Parker C, Omine M, Richards S, et al. for International PNH Interest Group. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood*. 2005;106:3699-3709. 10. Russo WF. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al, eds. *Hematology: Basic Principles and Practice*. 3rd ed. New York, NY: Churchill Livingstone; 2000:331-342. 11. Dacie JV, Lewis SM. Paroxysmal nocturnal haemoglobinuria: clinical manifestations, haematology, and natural of the disease. *Scr Haematol*. 1972;5:3-23. 12. Meyers G, Weitz J, Lamy T, et al. Disease-related symptoms reported across a broad population of patients with paroxysmal nocturnal hemoglobinuria. *Blood*. 2007;110: Abstract 3683. 13. Nishimura J-I, Kanakura Y, Ware RE, et al. Clinical course and flow cytometric analysis of paroxysmal nocturnal hemoglobinuria in the United States and Japan. *Medicine*. 2004;83:193-207. 14. Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal hemoglobinuria. *Br J Haematol*. 2007;137:181-192. 15. Dunn DE, Tanawattana-ron P, Boccuni P, et al. Paroxysmal nocturnal hemoglobinuria cells in patients with bone marrow failure syndromes. *Ann Intern Med*. 1999;131:401-408. 16. Rother RP, Bell L, Hillmen P, et al. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005;293:1653-1662. 17. Rother RP, Rollins SA, Mojcik CF, et al. *Nat Biotechnol*. 2007;25:1256-1264. [Published correction appears in *Nat Biotechnol*. 2007;25:1489]. 18. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al, eds. *Hematology: Basic Principles and Practice*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:15-42. 19. Richards SJ, Barnett D. The role of flow cytometry in the diagnosis of paroxysmal nocturnal hemoglobinuria in the clinical laboratory. *Clin Lab Med*. 2007;27:577-590. 20. Parker C. Paroxysmal nocturnal hemoglobinuria: an historical overview. *Hematology Am Soc Hematol Educ Program*. 2008;93:103. 21. Dolnik Z, Dostalkova D, Blahny J, et al. Paroxysmal nocturnal hemoglobinuria in a girl with hemolysis and "hematuria". *Pediatr Nephrol*. 2006;19:1177-1179. 22. Ballarín J, Acea Y, Torra Balcells R, et al. Acute renal failure associated to paroxysmal nocturnal haemoglobinuria leads to intratubular haemosiderin accumulation and CD163 expression. *Nephrol Dial Transplant*. 2011;26:3408-3411. 23. Sharma VR. Paroxysmal nocturnal hemoglobinuria: pathogenesis, testing, and diagnosis. *Clin Adv Hematol Oncol*. 2013;11:11-11. 24. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: myelodysplastic syndromes. version 2.2014. http://www.nccn.org/professionals/physician_glp/pdf/mlds.pdf. Accessed February 10, 2014. 25. Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. *Blood*. 2009;113:6522-6527. 26. Pelfaout de Lathur R, Mary J-Y, Salanoubat C, et al. on behalf of the French Society of Hematology and the French Association of Young Hematologists. Paroxysmal nocturnal hemoglobinuria: natural history of disease subtypes. *Blood*. 2008;112:3099-3106. 27. Mohanty BD, De Castro CM. Too many clots for comfort. *Am J Med*. 2012;125:243-245. 28. Meyers G, Parker C. Management issues in paroxysmal nocturnal hemoglobinuria. *Int J Hematol*. 2003;77:125-132. 29. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. *Blood*. 2013;121:4985-4996. 30. Brodsky A, Mazzocchi O, Sanchez F, et al. *Exp Hematol Oncol*. 2012;1:26.

Does your patient have PNH?

Early diagnosis is critical for improved patient prognosis^{1,2}

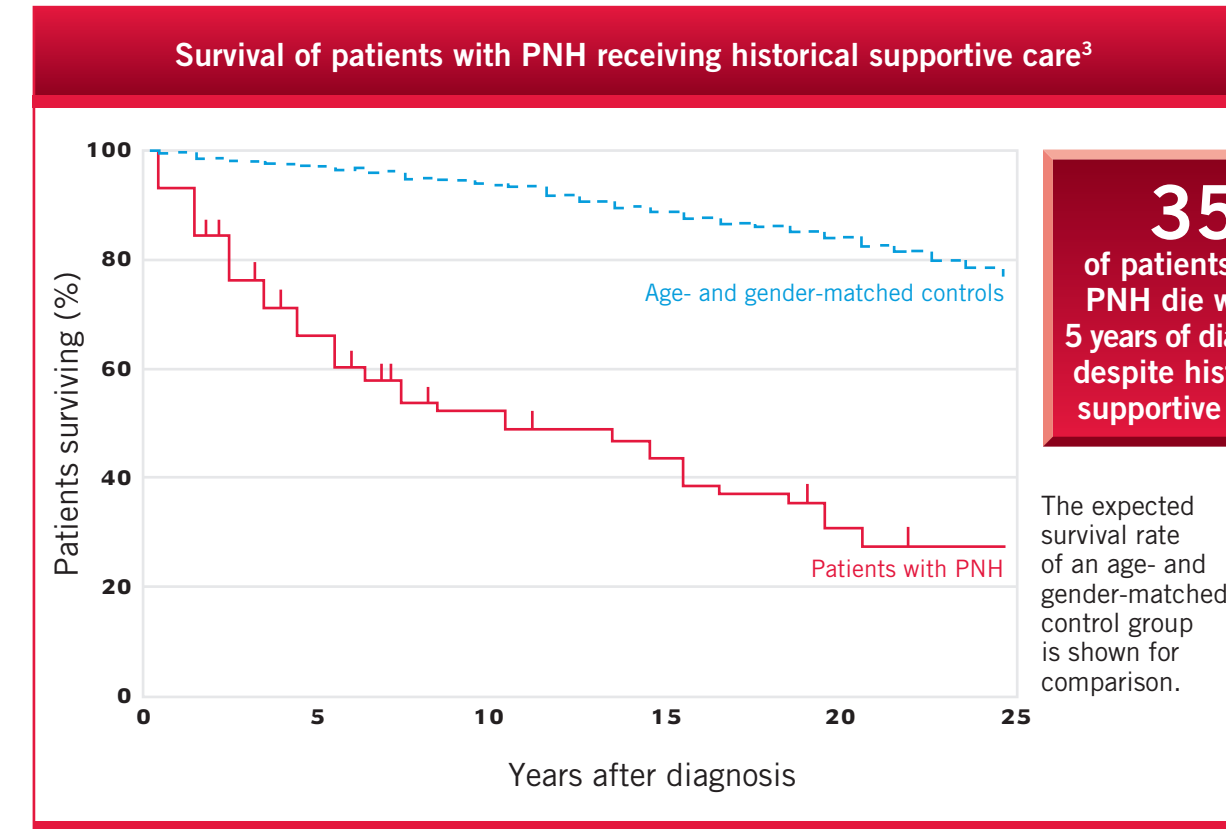
ALEXION

ALEXION

© 2015, Alexion Pharmaceuticals, Inc. All rights reserved. XXXX.XXXXXX

ALEXION

PNH is a progressive and life-threatening disease that can cause thrombosis, end organ damage, and increased mortality¹⁻⁵



*Study description: Researchers followed 80 consecutive patients with PNH referred to Hammersmith Hospital. They were treated with supportive measures, such as anticoagulation therapy after established thromboses and transfusions.

Chronic complement-mediated hemolysis is the underlying cause of progressive morbidities and mortality in patients with PNH⁴

- 40% to 67% of deaths in patients with PNH are caused by venous or arterial thrombosis⁶
- 64% of patients with PNH have chronic kidney disease (CKD), which is associated with premature mortality⁷
- Nearly 50% of patients with PNH have evidence of pulmonary hypertension (PHT)⁸

Monitor your high-risk patients for lab values and symptoms associated with PNH

Has your patient presented with any of the following conditions, signs, or symptoms? If so, *any* of these may raise the index of suspicion for PNH

<p>High-risk patient populations for PNH^{1,2}</p> <ul style="list-style-type: none"> • Coombs-negative hemolytic anemia, especially patients with concurrent iron deficiency,^{1,2} or • Hemoglobinuria (or “hematuria”),^{1,2} or • Aplastic anemia,^{1,2} or • RA-MDS,² or • Unexplained thrombosis,^{1,2} or • Unexplained cytopenia¹ 	<p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p>
<p>Any evidence of hemolysis³ (Normal ranges included in parentheses*)</p> <ul style="list-style-type: none"> • LDH $\geq 1.5 \times$ ULN (105-333 IU/L),^{4,5} or • Low haptoglobin levels¹⁶ (41-165 mg/dL), or • Elevated reticulocyte count⁵ (0.5-1.5%), or • Elevated bilirubin⁷ (0-0.3 mg/dL) 	<p>_____ IU/L</p> <p>_____ mg/dL</p> <p>_____ %</p> <p>_____ mg/dL</p>	
<p>Any signs of renal dysfunction and hemolysis⁸ (Normal ranges included in parentheses*)</p> <ul style="list-style-type: none"> • Proteinuria⁹ (≤ 30 mg albumin/g creatinine), or • Low eGFR⁸ (90-120 mL/min/1.73 m²), or • Elevated serum creatinine¹⁰ (female: 0.6-1.1 mg/dL; male: 0.7-1.3 mg/dL) 	<p>_____ mg/g</p> <p>_____ mL/min/1.73 m²</p> <p>_____ mg/dL</p>	
<p>Evidence of comorbidities with PNH¹¹ (Normal ranges included in parentheses*)</p> <ul style="list-style-type: none"> • Low platelet count¹² (100,000-400,000/μL), or • Elevated D-dimers¹³ (≤ 250 ng/mL), or • Elevated NT-proBNP¹⁴ (Normal ranges vary with both gender and age), or • Elevated pulmonary artery pressure¹⁴ (>25 mmHg) 	<p>_____ /μL</p> <p>_____ ng/mL</p> <p>_____ pg/mL</p> <p>_____ mmHg</p>	
<p>Other signs or symptoms associated with PNH that should raise the index of suspicion^{11,15-17}</p> <ul style="list-style-type: none"> • Abdominal pain • Chest pain • Dyspnea • Fatigue • Impaired health-related quality of life • Anemia • Dysphagia 	<p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p> <p>Yes <input type="checkbox"/></p>	<p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p> <p>No <input type="checkbox"/></p>

*Normal ranges from MedlinePlus, Medscape, and the Mayo Clinic Foundation. Normal ranges may vary slightly among different laboratories.

¹Low haptoglobin is indicative of excess plasma-free hemoglobin released from hemolysed RBCs.⁶

¹⁴A marker of cardiac dysfunction.¹⁴

High-sensitivity flow cytometry*—performed on peripheral blood—is the gold standard diagnostic test for PNH¹

- Flow cytometry is minimally invasive and relatively inexpensive
- Evaluation of RBCs alone may underreport clone size due to hemolysis and the dilution effect of transfusions^{1,2,18,19}
- Granulocytes give most accurate estimate of PNH clone size^{1,2,20}
 - FLAER/CD24 combinations recommended to detect PNH granulocytes²¹
- Low RBC clone size compared to WBC clone size indicative of intravascular hemolysis¹
- According to the ICCS guidelines, clear reporting of flow cytometry results is essential for appropriate clinical decisions¹

When ordering a PNH flow test, request^{1,21}:

- Clone size for each cell lineage (ie, granulocytes, monocytes, and erythrocytes) using >1 reagent
- For RBCs: proportion of type I (normal), II, and III cells
- Sensitivity level used (0.01% sensitivity is ideal)
- All previous flow results in order to monitor clonal expansion

<p>A PNH flow test should provide clone sizes for each cell lineage¹:</p> <ul style="list-style-type: none"> • Erythrocytes • Granulocytes • Monocytes 	<p>Type I___% Type II___% Type III___%</p> <p>_____ %</p> <p>_____ %</p>
---	--

*Detects PNH cells down to a 0.01% clone size.

References: 1. Borowitz MJ, Craig FE, DiGiuseppe JA, et al; for Clinical Cytometry Society. *Cytometry Part B*. 2010;78B:211-230. 2. Parker C, Omine M, Richards S, et al; for International PNH Interest Group. *Blood*. 2005;106:3699-3709. 3. Kim JS, Lee JW, Yoon S-S, et al. *Blood*. 2010;116: Abstract 4241. 4. Lee JW, Jang JH, Kim JS, et al. *Blood*. 2011;118: Abstract 3166. 5. Kato GJ, McGowan V, Machado RF, et al. *Blood*. 2006;107:2279-2285. 6. Rother RP, Bell L, Hillmen P, et al. *JAMA*. 2005;293:1653-1662. 7. Milton JN, Sebastiani P, Solovieff N, et al. *PLoS ONE*. 2012;7:e34741. 8. Kim JS, Jang JH, Lee JW, et al. Renal impairment is a risk factor for early mortality in patients with paroxysmal nocturnal hemoglobinuria (PNH). In: Posters of the 16th Congress of the European Hematology Association; June 9-12, 2011; London, United Kingdom. Abstract 0271. 9. Stevens LA, Coresh J, Greene T, et al. *N Engl J Med*. 2006;354:2473-2483. 10. Baumgarten M, Gehr T. *Am Fam Physician*. 2011;84:1138-1148. 11. Lee JW, Jang JH, Kim JS, et al. *Int J Hematol*. 2013;97:749-757. 12. Veneri D, Franchini M, Randon F, et al. *Blood Transfus*. 2009;7:75-85. 13. Caprini JA, Glase CJ, Anderson CB, et al. *Circulation*. 2004;109:I-4-I-8. 14. Hill A, Rother RP, Wang X, et al. *Br J Haematol*. 2010;149:414-425. 15. Rachidi S, Musallam KM, Taher AT. *Eur J Intern Med*. 2010;21:260-267. 16. Hill A, Richards SJ, Hillmen P. *Br J Haematol*. 2007;137:181-192. 17. Moyo VM, Mukhina GL, Garrett ES, et al. *Br J Haematol*. 2004;126:133-138. 18. Hochsmann B, Rojewski M, Schrezenmeier H. *Ann Hematol*. 2011;90:887-899. 19. Sutherland DR, Kuek N, Azcona-Olivera J, et al. *Am J Clin Pathol*. 2009;132:564-572. 20. Brodsky RA. *Blood*. 2009;113:6522-6527. 21. Sutherland DR, Keeney M, Illingworth A. *Cytometry Part B*. 2012;82B:195-208.