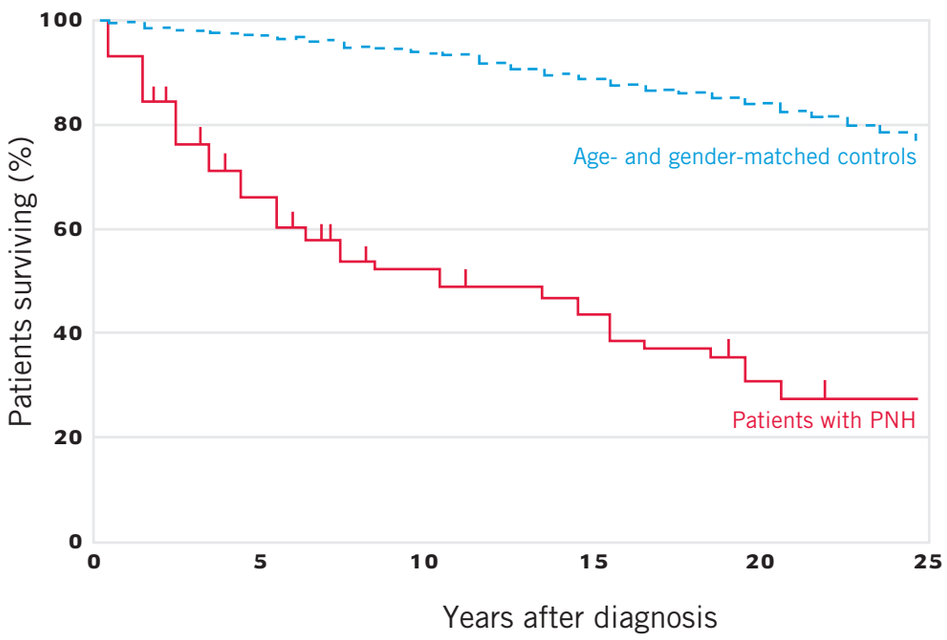
Does your patient have Paroxysmal Nocturnal Hemoglobinuria (PNH)?

Early diagnosis is critical for improved patient prognosis[1,2]

PNH is a progressive and life-threatening disease that can cause thrombosis, end-organ damage, and increased mortality[1-5]

Survival of patients with PNH receiving historical supportive care[3]



35% of patients with PNH die within 5 years of diagnosis despite historical supportive care*[3]

The expected survival rate of an age- and gender-matched control group is shown for comparison.

***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 premature mortality in patients with PNH[4]

- 40% to 67% of deaths in patients with PNH are caused by venous or arterial thrombosis[6]
- 64% of patients with PNH have chronic kidney disease (CKD), which in later stages is associated with premature mortality[7,8]
- Nearly 50% of patients with PNH have evidence of pulmonary hypertension (PHT)[9]

The diverse and common symptomatology of PNH can delay diagnosis[10,11]

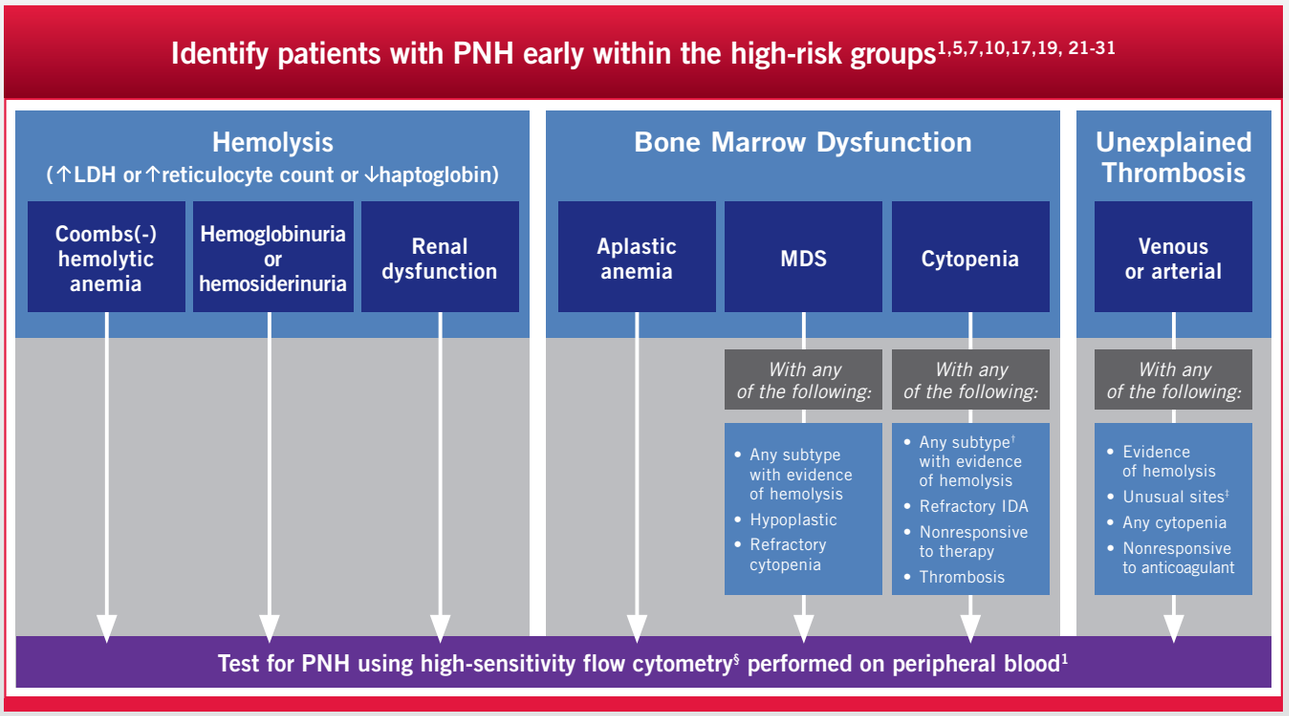
- Diagnosis typically delayed from 1 to more than 10 years[12]
- Nearly three-fourths of patients with PNH do not present with hemoglobinuria[10]
- Diverse symptomatology of PNH drives the need for a comprehensive clinical assessment and routine diagnostic approach[9,10,13-15]

Identification of PNH cells has important prognostic and therapeutic implications[10,16]

- The International Clinical Cytometry Society (ICCS) and International PNH Interest Group (IPIG) recommend continued monitoring of patients at high risk for PNH[1,10]
- High-sensitivity flow cytometry* (HSFC)—performed on peripheral blood—is the gold standard diagnostic test for PNH[1]

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

Early diagnosis is essential for improved patient management and prognosis[1,17-20]



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 (ICCS) guidelines and other expert findings suggest that the clinical presentations outlined above increase the likelihood of PNH[1,5,7,10,17,19, 21-31]

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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

High-risk patient populations for PNH[1,2]		
• Coombs-negative hemolytic anemia, especially patients with concurrent iron deficiency,[1,2] or	Yes ☐	No ☐
• Hemoglobinuria (or "hemosiderinuria"),[1,2] or	Yes ☐	No ☐
• Renal dysfunction with hemolysis,[3] or	Yes ☐	No ☐
• Aplastic anemia,[1,2] or	Yes ☐	No ☐
• RA-MDS,[2] or	Yes ☐	No ☐
• Unexplained thrombosis,[1,2] or	Yes ☐	No ☐
• Unexplained cytopenia[1]	Yes ☐	No ☐
Any evidence of hemolysis[4] (Normal ranges included in parentheses*)		
• LDH ≥1.5 x ULN (105-333 IU/L),[5,6] or	_____ IU/L	
• Low haptoglobin levels†[7] (41-165 mg/dL), or	_____ mg/dL	
• Elevated reticulocyte count[6] (0.5-1.5%), or	_____ %	
• Elevated bilirubin[8] (direct: 0-0.3 mg/dL, total: 0.3-1.9 mg/dL)	_____ mg/dL	
Any signs of renal dysfunction and hemolysis[3] (Normal ranges included in parentheses*)		
• Proteinuria[9] (≤30 mg albumin/g creatinine), or	_____ mg/g	
• Low eGFR[3] (90-120 mL/min/1.73 m^2), or	_____ mL/min/1.73 m^2	
• Elevated serum creatinine[10] (female: 0.6-1.1 mg/dL; male: 0.7-1.3 mg/dL)	_____ mg/dL	
Evidence of comorbidities with PNH[11] (Normal ranges included in parentheses*)		
• Low platelet count[12] (150,000-400,000/μL), or	_____ /μL	
• Elevated D-dimers[13] (≤250 ng/mL), or	_____ ng/mL	
• Elevated NT-proBNP‡[14] (Normal ranges vary with both gender and age), or	_____ pg/mL	
• Elevated pulmonary artery pressure[14] (<25 mmHg)	_____ mmHg	
Other signs or symptoms associated with PNH that could raise the index of suspicion[11,15-17]		
• Abdominal pain	Yes ☐	No ☐
• Chest pain	Yes ☐	No ☐
• Dyspnea	Yes ☐	No ☐
• Fatigue	Yes ☐	No ☐
• Impaired health-related quality of life	Yes ☐	No ☐
• Anemia	Yes ☐	No ☐
• Dysphagia	Yes ☐	No ☐

*Normal ranges from MedlinePlus, Medscape, and the Mayo Clinic Foundation. Normal ranges may vary slightly among different laboratories.
†Low haptoglobin is indicative of excess plasma-free hemoglobin released from hemolysed RBCs.[7]
‡NT-proBNP = N-terminal pro-brain natriuretic peptide, a marker of cardiac dysfunction.[14]

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High-sensitivity flow cytometry (HSFC)*—performed on peripheral blood—is the gold standard diagnostic test for PNH[1,18]

- Flow cytometry is minimally invasive and relatively inexpensive
- Labs should perform PNH HSFC on white blood cells (WBCs) and on red blood cells (RBCs)
- Evaluation of RBCs alone may underreport clone size due to hemolysis and the dilution effect of transfusions[1,2,19,20]
- Granulocytes give most accurate estimate of PNH clone size[1,2,21]
- Low RBC clone size compared to WBC clone size indicative of intravascular hemolysis[1]
- According to the ICCS guidelines, clear reporting of flow cytometry results is essential for appropriate clinical decisions[1]

When ordering a PNH flow test, request[1,22]:

- 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

A PNH flow test should provide clone sizes for each cell lineage[1]:	
• Erythrocytes	Type I___% Type II___% Type III___%
• Granulocytes	_____ %
• Monocytes	_____ %

*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 the International PNH Interest Group. *Blood*. 2005;106:3699-3709. **3.** 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. **4.** Kim JS, Lee JW, Yoon S-S, et al. *Blood*. 2010;116: Abstract 4241. **5.** Lee JW, Jang JH, Kim JS, et al. *Blood*. 2011;118: Abstract 3166. **6.** Kato GJ, McGowan V, Machado RF, et al. *Blood*. 2006;107:2279-2285. **7.** Rother RP, Bell L, Hillmen P, et al. *JAMA*. 2005;293:1653-1662. **8.** Milton JN, Sebastiani P, Solovieff N, et al. *PLOS ONE*. 2012;7:e34741. **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.** Sharma VR. Paroxysmal nocturnal hemoglobinuria: pathogenesis, testing, and diagnosis. *Clin Adv Hematol Oncol*. 2013;11:1-11. **19.** Hochsmann B, Rojewski M, Schrezenmeier H. *Ann Hematol*. 2011;90:887-899. **20.** Sutherland DR, Kuek N, Azcona-Olivera J, et al. *Am J Clin Pathol*. 2009;132:564-572. **21.** Brodsky RA. *Blood*. 2009;113:6522-6527. **22.** Sutherland DR, Keeney M, Illingworth A. *Cytometry Part B*. 2012;82B:195-208.

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