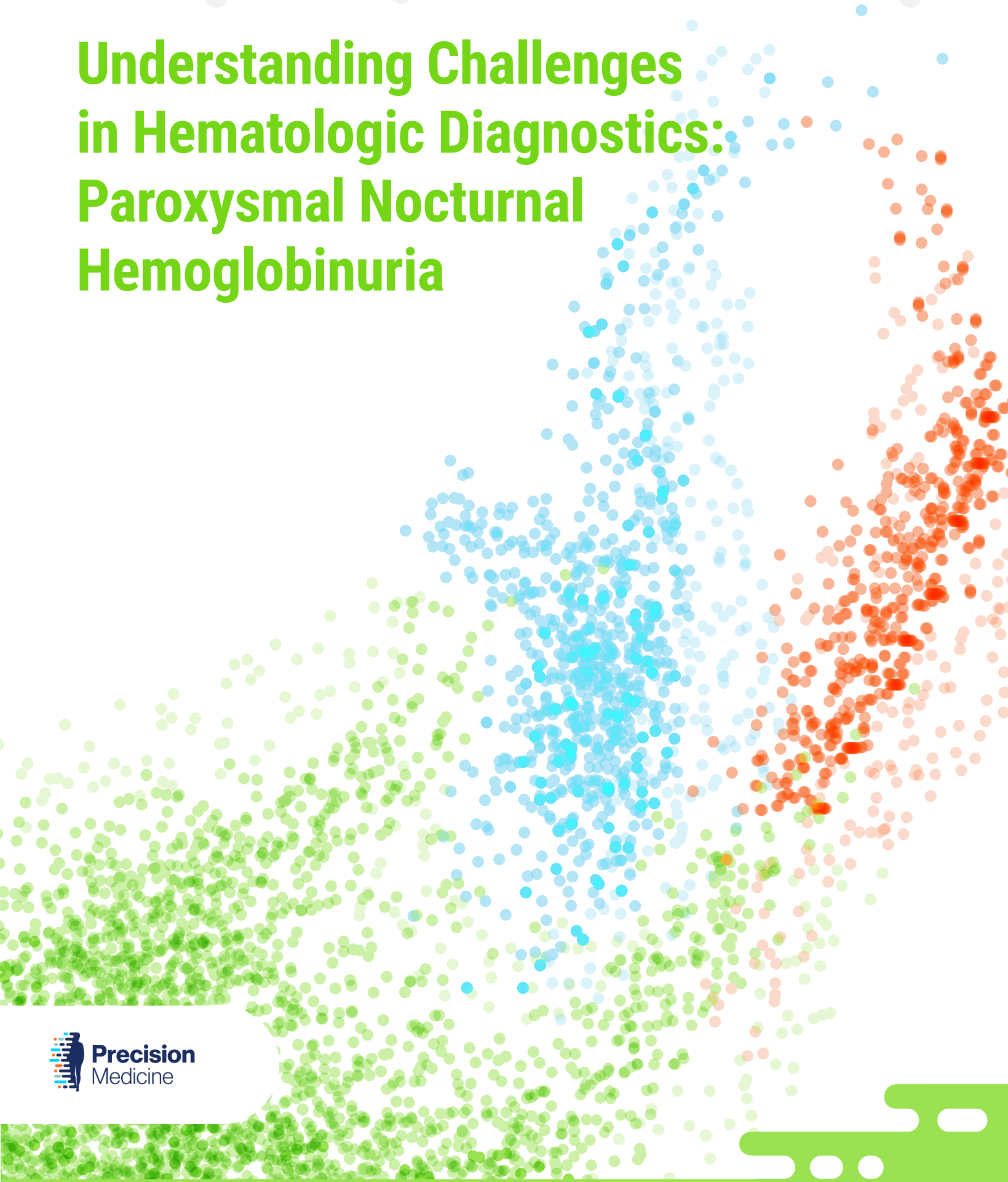
Understanding Challenges in Hematologic Diagnostics: Paroxysmal Nocturnal Hemoglobinuria



Precision Medicine

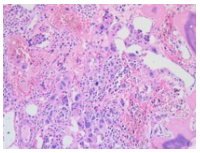
THE IMPORTANCE OF A CORRECT DIAGNOSIS IN HEMATOLOGY

Many **hematologic diseases** have **similar symptoms but vastly different treatments**, making an **accurate diagnosis essential**[1-3]

→

Biomarker testing is a fundamental component of the diagnostic workup **for hematologic diseases**[1-6]

Key diagnostic biomarker testing technologies in hematology[1-4]



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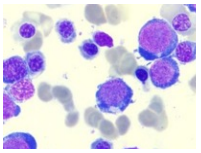
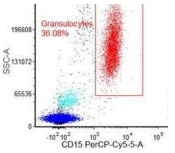


Cytology[8]



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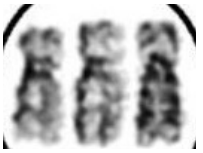
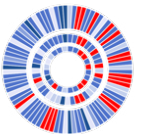
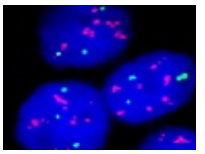


Karyotyping[10]



NGS[11]



FISH[12]

CHALLENGES IN DIAGNOSING PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) REFLECTS DIAGNOSTIC CHALLENGES IN HEMATOLOGY[1-3]

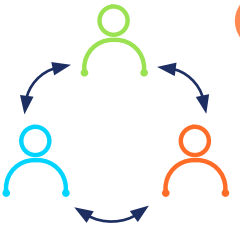
Patients with PNH often present with symptoms similar to those of aplastic anemia (AA) and myelodysplastic syndrome (MDS)[1-3]

Common PNH signs and symptoms[1,13]

- Hemoglobinuria
- Kidney disease/ impaired renal function
- Abdominal pain
- Dysphagia
- Erectile dysfunction
- History of thromboembolism
- Dyspnea
- Fatigue

Common AA signs and symptoms[2,14]

- Progressive weakness
- Infections
- Petechiae
- Pallor
- Dizziness
- Fatigue
- Unexplained bruising/bleeding
- Dyspnea
- Fever



Common MDS signs and symptoms[3]

- Chest pain
- Infections
- Petechiae
- Pallor
- Dizziness
- Fatigue
- Unexplained bruising/bleeding
- Dyspnea

PNH is not mutually exclusive with BMF[1]

Patients with PNH, PNH and a BMF disorder, AA, or MDS may present with only a few symptoms or with additional symptoms not listed above[1-4, 13-15]

Biomarker testing can help diagnose patients[1-4]

MDS and AA are mostly diagnosed by hematology tests, cell morphology, bone marrow biopsy, and cytogenetics; PNH is primarily diagnosed with flow cytometry

AA, aplastic anemia; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndrome; NGS, next-generation sequencing; PNH, paroxysmal nocturnal hemoglobinuria; TE, thromboembolism.

References: 1. Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK562292/ **2.** Moore CA, Krishnan K. Aplastic anemia. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534212/ **3.** Dotson JL, Lebowicz Y. Myelodysplastic syndrome. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534126/ **4.** Bonadies N et al. *J Clin Med*. 2021;10(5):1026. doi:10.3390/jcm10051026 **5.** Gnanaraj J et.al. *Blood Review*. 2018. doi:10.1016/j.blre.2018.03.001 **6.** Bluteau O et. al. *Blood*. 2018;131(7):717-732. doi: 10.1182/blood-2017-09-806489 **7.** This image was originally published in ASH Image Bank. Hussein Said Baden. Myelofibrosis associated osteomyelosclerosis - 3. ASH Image Bank. 2009; #00003928. © the American Society of Hematology. **8.** This image was originally published in ASH Image Bank. Ke Xu, MD. MDS with multilineage dysplasia. ASH Image Bank. 2022; #00063919. © the American Society of Hematology. **9.** Illingworth A et al. *Cytometry B Clin Cytom*. 2018;94(1):49-66. doi:10.1002/cyto.b.21609 **10.** This image was originally published in ASH Image Bank. Mr Anil Kuman Yadav; Dr Manorama Bhargava. Extra Philadelphia chromosomal karyotype with gain of chromosome 6, 8, and 19 in CML-Myeloid BC. ASH Image Bank. 2018; #00061437. © the American Society of Hematology. **11.** Cheng H et al. *Cell Rep*. 2018;25(5):1332-1345, e1-e5. doi:10.1016/j.celrep.2018.10.007 **12.** Yu J et al. *Sci Rep*. 2019;9(1):7518. doi:10.1038/s41598-019-44015-7 **13.** Schrezenmeier H et al. *Ann Hematol*. 2020;99(7):1505-1514. doi:10.1007/s00277-020-04052-z **14.** Ahmed P et al. *Hematology*. 2020;25(1):48-54. doi: 10.1080/16078454.2019.1711344 **15.** Foran JM et al. *Am J Med*. 2012;125(7 Suppl):S6-13. doi: 10.1016/j.amjmed.2012.04.015

A SUBSTANTIAL NUMBER OF PATIENTS ARE POSITIVE FOR PNH AND BMF[1]

BMF

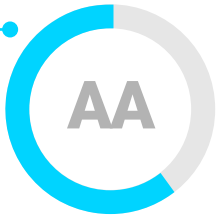
~63%

of patients with PNH have a history of BMF[2]

PNH

50%-61%

of patients with AA are positive for PNH[3,4]



PNH

10%-20%

of patients with MDS are positive for PNH[3,5]

Patients with both PNH and BMF may have[3]:

- ↑ LDH
- ↓ hemoglobin
- ↑ reticulocytes
- ↑ thrombocytopenias

Changes in the disease course may vary by the specific disease that overlaps with PNH[3]

In all PNH patients, including those with concomitant BMF, PNH clone size correlates with risk of thrombotic events[3]

Case reports suggest that patients with myelofibrosis can be positive for PNH; the precise incidence of clinical PNH is not known but is thought to be rare[1,3,4]

PREVALENCE OF SELECT SYMPTOMS COMMON IN PNH, AA, AND MDS AT DIAGNOSIS

	PNH[2,6,7]	AA[8]	MDS[9,10]
Fatigue	81%	81%	80%-85%
Infection/fever	–	69%	40%-50%
Unexplained bruising/bleeding	64%	60%	30%-65%
Dyspnea	45%	43%	–

LDH, lactate dehydrogenase; MF, myelofibrosis.

References: 1. Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK562292/ **2.** Schrezenmeier H et al. *Ann Hematol.* 2020;99(7):1505-1514. doi:10.1007/s00277-020-04052-z **3.** Fattizzo B et al. *Leukemia*. 2021;35(11):3223-3231. doi:10.1038/s41375-021-01190-9 **4.** Babushok DV. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):143-152. doi:10.1182/hematology.2021000245 **5.** Wong SA et al. *Curr Oncol*. 2018;25(5):e391-e397. doi:10.3747/co.25.4018 **6.** Moore CA, Krishnan K. Aplastic anemia. In: StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK534212/. Accessed September 18, 2023. **7.** Devos T et al. *Eur J Haematol*. 2018;101(6):737-749. doi:10.1111/ejh.13166 **8.** Ahmed P et al. *Hematology*. 2020;25(1):48-54. doi:10.1080/16078454.2019.1711344 **9.** Bonadies N et al. *J Clin Med*. 2021;10(5):1026. doi:10.3390/jcm10051026 **10.** Foran JM, Shammo JM. *Am J Med*. 2012;125(7)(suppl):S6-S13. doi:10.1016/j.amjmed.2012.04.015

A COMPLETE AND CORRECT DIAGNOSIS IS FUNDAMENTAL TO MAKING TREATMENT DECISIONS IN PNH, AA, AND MDS

A complete diagnosis for patients with PNH, AA, and MDS can inform treatment decisions

Untreated PNH	**Consequences including RBC transfusions and organ damage, among others[1,2]**
Untreated AA	**Serious complications associated with high mortality rate[3,4]**
Untreated MDS	**Life-threatening BMF/progression to acute myeloid leukemia[5-8]**

A complete diagnosis for patients with PNH, AA, and MDS can inform treatment decisions

Compared to healthy individuals, patients with PNH alone have:
- Increased risk for thrombotic events[1,9]
- **6X** greater risk of kidney damage, leading to chronic kidney disease[2,10]

Compared to patients with AA only, patients positive for AA and PNH have:
- Higher response rates to standard treatments for AA[11]
- Higher failure-free survival rates[12]

Compared to patients with MDS alone, patients positive for MDS and PNH have:
- Higher response rates to standard MDS treatments
- Increased rate of thrombotic events[11]

Flow cytometry is the gold standard test to identify patients with PNH[13-15]

- **There are 2 different types of flow cytometry assays that can detect the absence of GPI-anchored proteins, which is the cause of PNH**
- **For a confirmed diagnosis, it is important to test at least two distinct cell lineages, preferably erythrocytes and granulocytes/monocytes**

PNH clone size refers to the percentage of cells *deficient* in GPI-anchored proteins

		Standard Sensitivity	High Sensitivity
Gating	RBCs	Forward scatter vs side scatter (log mode)	CD235a-labeled cells
	WBCs	Forward scatter vs side scatter (linear mode)	Neutrophils: CD15-labeled cells Monocytes: CD64-labeled cells
Cell markers	RBCs	CD55[a] and/or CD59[a]	CD235a and CD59
	WBCs	CD55[a] and/or CD59[a]	Neutrophils: CD15, CD45, CD24,[a] and FLAER[b] Monocytes: CD64, CD45, CD14,[a] and FLAER[b]
Limit of detection[c]		4%	0.05%

[a]GPI-anchored protein.
[b]Labeling method that detects all GPI-anchored proteins.
[c]Based on the smallest PNH clone that can be reliably detected.

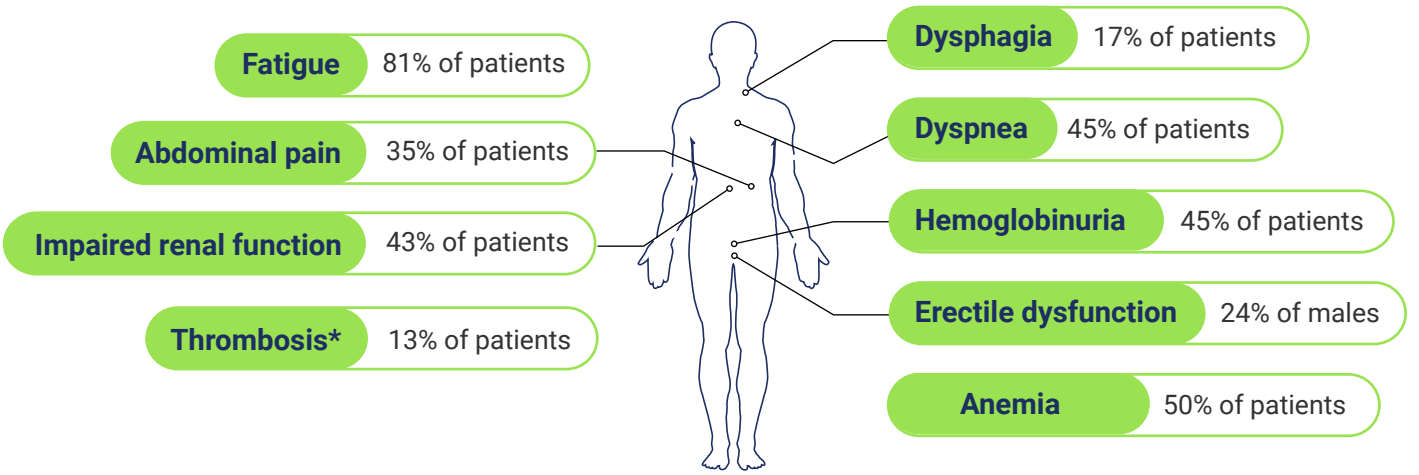
CD, cluster of differentiation; FLAER, fluorescent proaerolysin; GPI, glycosylphosphatidylinositol; RBCs, red blood cells; WBCs, white blood cells.

References: 1. Schrezenmeier H et al. *Ann Hematol*. 2020;99(7):1505-1514. doi:10.1007/s00277-020-04052-z **2.** Kokoris SI et al. *Hematology*. 2018;23(8):558-566. doi:10.1080/10245332.2018.1444563 **3.** Olson TS. Accessed September 18, 2023. https://www.uptodate.com/contents/aplastic-anemia-pathogenesis-clinical-manifestations-and-diagnosis **4.** Camitta BM et al. *Blood*. 1979;53(3):504-514. doi:10.1182/blood.V53.3.504.504 **5.** Toma A et al. *Haematologica*. 2012;97(10):1459-1470. doi:10.3324/haematol.2012.063420 **6.** Dayyani F et al. *Cancer*. 2010;116(9):2174-2179. doi:10.1002/cncr.24984 **7.** Nachtkamp K et al. *Ann Hematol*. 2016;95(6):937-944. doi:10.1007/s00277-016-2649-3 **8.** Jain AG et al. ASH 2021. Poster 2600. doi:10.1182/blood-2021-149708 **9.** Richards SJ et al. *Br J Haematol*. 2020;189(5):954-966. doi:10.1111/bjh.16427 **10.** Brodsky RA. Blood. 2014;124(18):2804-2811. doi:10.1182/blood-2014-02-522128 **11.** Fattizzo B et al. *Leukemia*. 2021;35(11):3223-3231. doi:10.1038/s41375-021-01190-9 **12.** Sugimori C et al. *Blood*. 2006;107(4):1308-1314. doi: 10.1182/blood-2005-06-2485 **13.** Sutherland DR et al. *Cytometry B Clin Cytom*. 2018;94(1):23-48. doi:10.1002/cyto.b.21610 **14.** Illingworth A et al. *Cytometry B Clin Cytom*. 2018;94(1):49-66. doi:10.1002/cyto.b.21609 **15.** Bektas M et al. *J Manag Care Spec Pharm*. 2020;26(12-b Suppl):S8-S14. doi: 10.18553/jmcp.2020.26.12-b.s8

WHEN TO TEST FOR PNH WITH FLOW CYTOMETRY

PNH presentation is highly variable, and an accurate diagnosis takes 2 years on average[1,2]

Most common symptoms for PNH include[3]:



Patients may not present with all symptoms[1,3]

PNH clone size at diagnosis positively correlates with symptom burden and thrombotic risk[4,5]

If your patient has some or all of these symptoms, consider biomarker testing for PNH with flow cytometry. For all your patients, remember to:

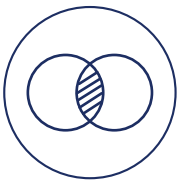
- **C**oombs-negative hemolytic anemia
- **H**emoglobinuria
- **E**rectile dysfunction
- **C**ytopenias
- **K**idney disease/impaired renal function
- **Th**rombosis at unusual sites
- **A**nemia
- **T**iredness

Get definitive answers and test early.

*Thrombosis typically occurs in unusual site

References: 1. Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria. In: *StatPearls.* StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK562292/ **2.** Shammo JM et al. ASH 2015. Poster 3264. doi:10.1182/blood.V126.23.3264.3264 **3.** Schrezenmeier H et al. *Ann Hematol*. 2020;99(7):1505-1514. doi:10.1007/s00277-020-04052-z **4.** Fattizzo B et al. *Leukemia.* 2021;35(11):3223-3231. doi:10.1038/s41375-021-01190-9 **5.** Richards SJ et al. *Br J Haematol.* 2020;189(5):954-966. doi:10.1111/bjh.16427

SUMMARY



In hematology, symptom overlap makes diagnosis challenging[1-3]

- PNH, AA, and MDS have similar symptoms but drastically different prognoses and treatment options

Diagnostic biomarker testing is fundamental to getting an accurate and complete diagnosis[4]

- Flow cytometry is the only test that can differentiate PNH from AA and MDS[5,6]
- For all your patients, remember to **CHECK ThAT** and consider testing for PNH with flow cytometry

References: 1. Moore CA, Krishnan K. Aplastic anemia. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534212/ **2.** Dotson JL, Lebowicz Y. Myelodysplastic syndrome. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK534126/**3.** Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 18, 2023. https://www.ncbi.nlm.nih.gov/books/NBK562292/ **4.** Bonadies N et al. *J Clin Med*. 2021;10(5):1026. doi:10.3390/jcm10051026 **5.** Sutherland DR et al. *Cytometry B Clin Cytom*. 2018;94(1):23-48. doi:10.1002/cyto.b.21610 **6.** Illingworth A et al. *Cytometry B Clin Cytom*. 2018;94(1):49-66. doi:10.1002/cyto.b.21609

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