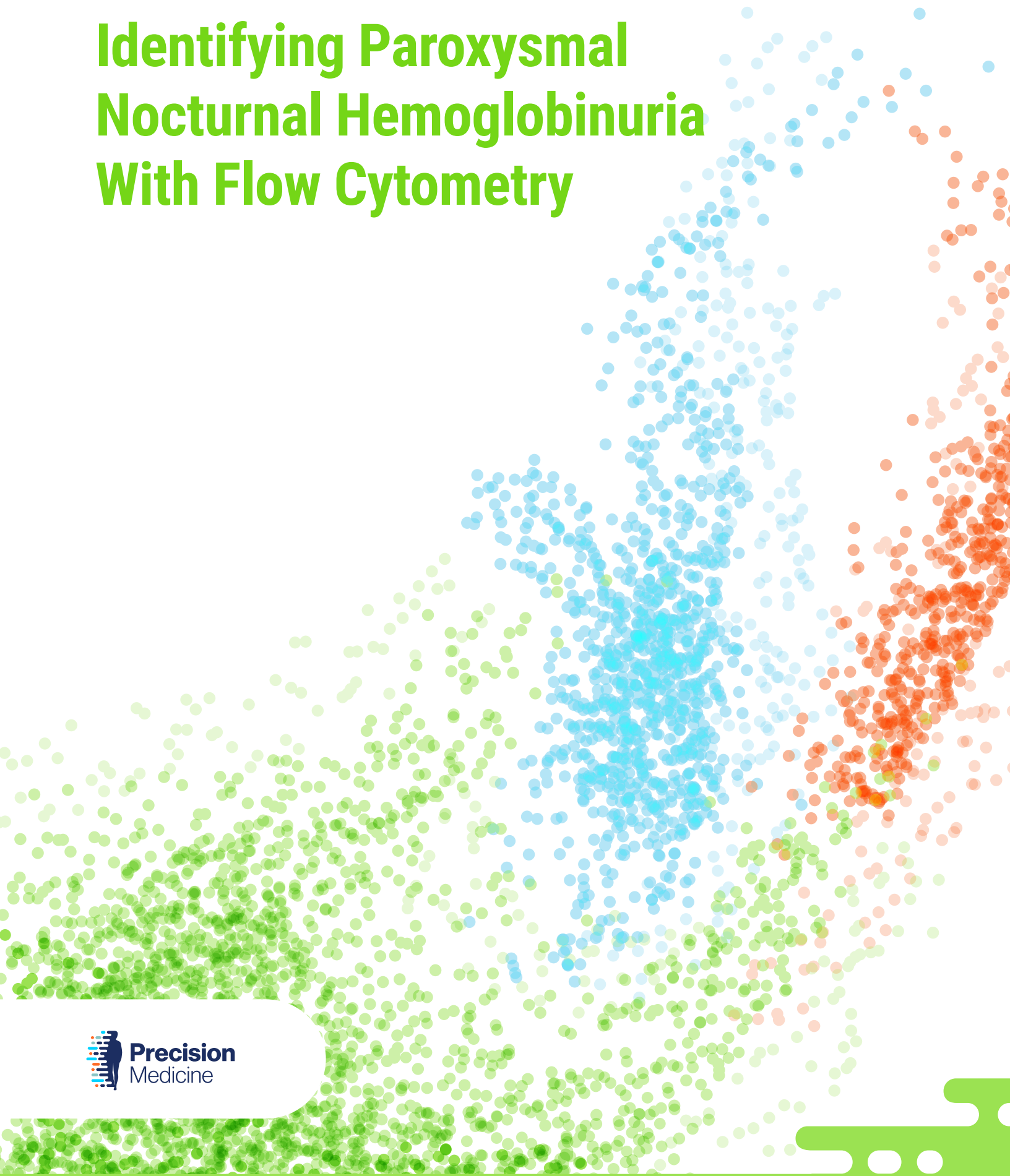
# Identifying Paroxysmal Nocturnal Hemoglobinuria With Flow Cytometry



Precision Medicine

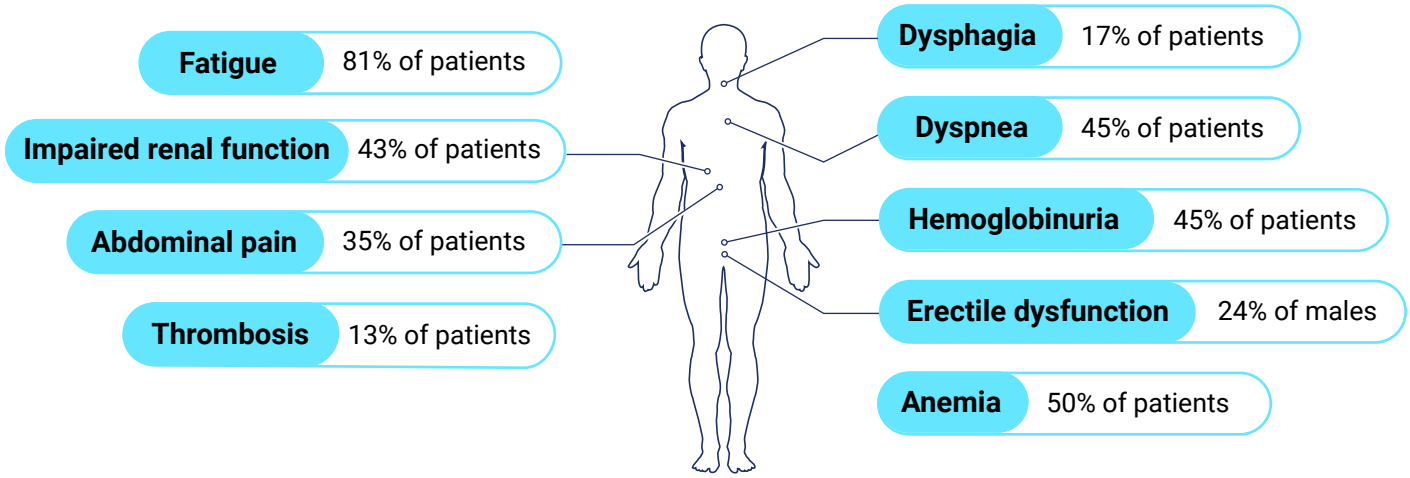
# PAROXYSMAL NOCTURNAL HEMOGLOBINURIA OVERVIEW

## PNH is a rare hematologic disorder with variable clinical presentation[1,2]

The estimated global prevalence of PNH is **10 to 20** per million[1]

The estimated global incidence of PNH is **≈1 to 2** per million[1]

Common signs and symptoms for PNH include:[2]




## Diversity of symptoms and patient presentation contributes to diagnostic delays[3,4]

In one study which surveyed 163 patients with PNH[4,5]:

**<40%**
of patients were diagnosed within 12 months of symptom onset

**≈38%**
of patients saw ≥5 HCPs prior to diagnosis

**24%**
of patients were diagnosed after >5 years

# IMPORTANCE OF A TIMELY DIAGNOSIS

Patients with PNH, before diagnosis, can experience an extensive history of complications including[2]:

- **61%** history of RBC transfusions[2]
- **19%** thrombosis and other major vascular events[2]

PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

# A CORRECT DIAGNOSIS IS FUNDAMENTAL TO MAKING APPROPRIATE TREATMENT DECISIONS IN PNH

Many hematologic diseases have similar symptoms but vastly different treatments, making an accurate and timely diagnosis essential[3,6,7]

- PNH symptoms often overlap those of AA and myelodysplastic syndrome, as they can be associated with each other
- PNH is not mutually exclusive with BMF disorders

**PNH can affect both males and females equally, with a median age of 36 years at disease onset[1,2]**

## PNH is a rare hematologic disorder with variable signs and symptoms[1,2]

| Category | Hemolysis | Treatment strategy | Typical clone size* |
|---|---|---|---|
| **Classic PNH** | High | PNH-specific therapy | Large (>50%) |
| **PNH in the setting of another specified bone marrow disorder[a]** | Low | Treat underlying disease; patients with large clones may benefit from complement inhibitors | Variable (usually relatively small, <50%) |
| **Subclinical PNH** | Absent | Treat underlying disease (MDS, AA) | Small (<10%) |

**Biomarker testing is a fundamental component of the diagnostic workup for hematologic diseases[3,6-8]**

# PNH IS A RARE BUT TREATABLE DISEASE

## Make Sure Your Patients Don't Wait Years for a Diagnosis

**For all your patients, remember to[1,2,b]:**

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

**If your patient has some or all of these symptoms, consider biomarker testing for PNH with flow cytometry**

*PMN clone size.
[a]AA or low-risk myelodysplastic syndrome.
[b]This list does not include all possible symptoms associated with PNH.
AA, aplastic anemia; BMF, bone marrow failure; MDS, myelodysplastic syndrome.

# FLOW CYTOMETRY ASSAYS CAN DETECT THE ABSENCE OF GPI-ANCHORED PROTEINS, INCLUDING CD55 AND CD59

## PNH is caused by acquired *PIG-A* gene mutations, resulting in the loss of GPI-anchored complement regulatory proteins[9-11]

*PIG-A* encodes for a protein required for biosynthesis of GPI anchors[9,12]

+

GPI anchors attach GPI-anchored proteins to the cell surface[9,13]

=

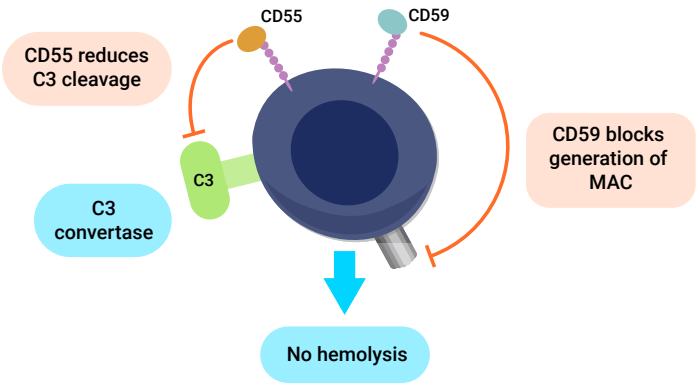
*PIG-A* mutation results in a loss of the GPI anchor and the associated GPI-anchored protein (eg, CD55, CD59) from the cell surface[9-13]

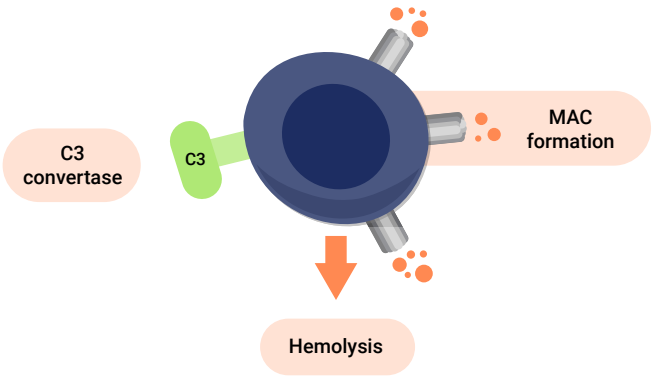
**Because the *PIG-A* mutation occurs in a hematopoietic stem cell, blood cells derived from that mutant stem cell also lack GPI-anchored proteins[9,10,14]**

**Presence of a PIG-A mutation does not confirm PNH; flow cytometry is the gold standard test for a definitive diagnosis of PNH[3,9]**

### Without PNH

In normal RBCs, the GPI-anchored complement regulatory proteins CD55 and CD59 protect the RBC from complement-mediated hemolysis[9, 15-18]



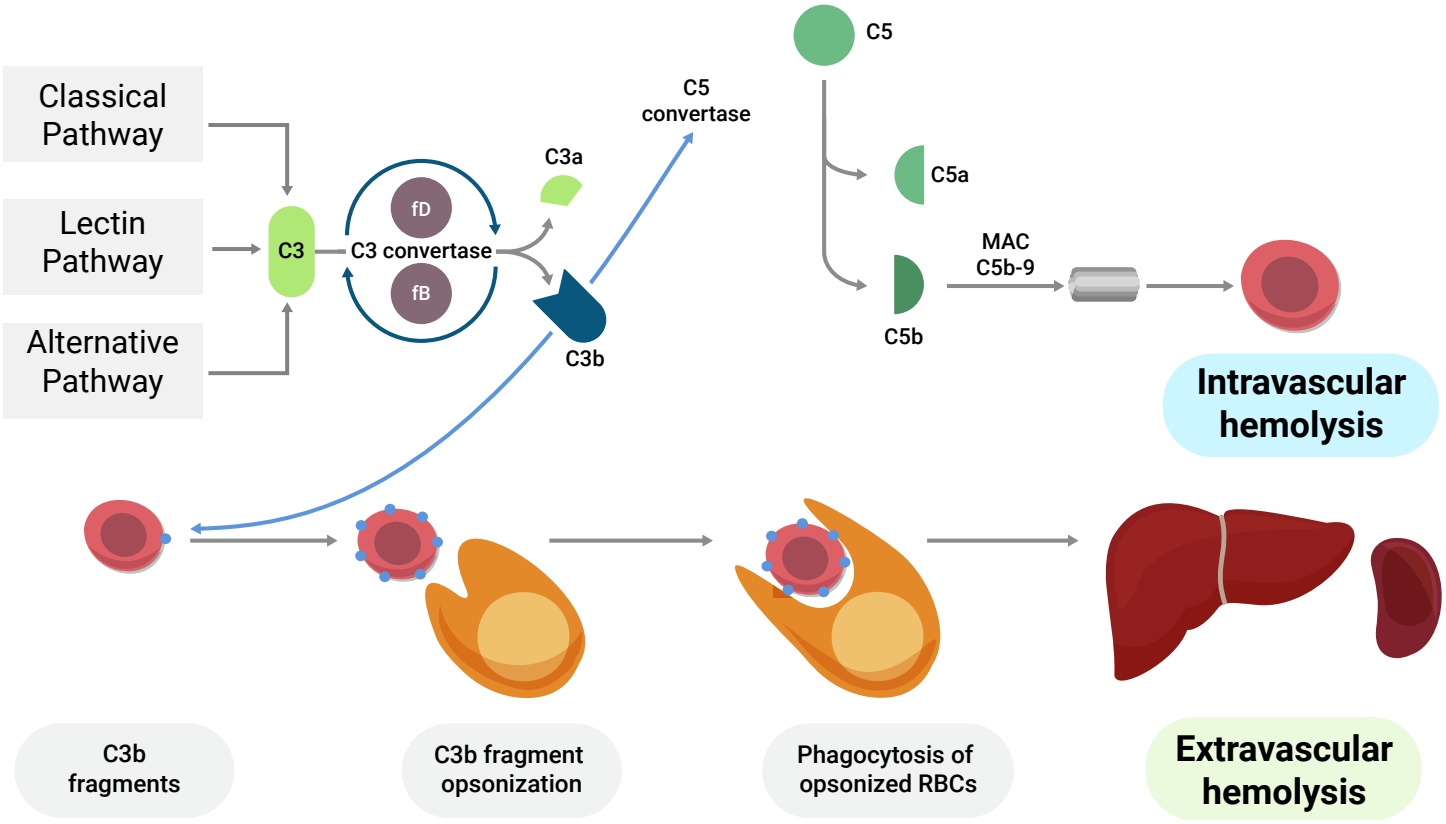




### With PNH

In PNH, the acquired *PIG-A* mutation leads to a lack of CD55 and CD59 on the RBC surface, exposing the RBCs to complement-mediated hemolysis[9-11,15-18]

C, complement component; CD, cluster of differentiation; GPI, glycosylphosphatidylinositol; MAC, membrane attack complex; RBC, red blood cell.

## Complement-mediated hemolysis occurs via 2 mechanisms[9,19,20]




**IVH**[9,19]
PNH RBCs are destroyed within the blood vessels by the formation of the MAC

**EVH**[9,19]
The deposition of C3 fragments on PNH RBCs tags them for destruction by spleen and liver macrophages

**Once suspected based on clinical and laboratory evaluation, PNH can be definitively diagnosed using flow cytometry**[21]

fB, factor B; fD, factor D.

# DIAGNOSING PNH WITH FLOW CYTOMETRY

PNH should be diagnosed based on the absence or severe deficiency of GPI-anchored proteins on ≥2 peripheral blood cell lineages[1,9,22]

Flow cytometry estimates the PNH clone size—the percentage of cells that lack GPI-anchored proteins[22,23]

- PNH clone size at diagnosis positively correlates with symptom burden[24,25]
- Patients with classic PNH typically have clone sizes of >50%; patients with PNH with other BMF disorder, <50%; and patients with subclinical PNH, <10%[21]

Proteins that can be assayed include[1,23]:

- GPI-anchored proteins (CD59, CD55, CD14, and CD24)
- Cell lineage markers (CD15, CD16, CD45, and CD64)

Both RBCs and WBCs should be analyzed[21,22]

- WBC analysis (eg, FLAER) more accurately determines clone size
- Hemolysis and transfusion can lead to underestimation with RBC analysis alone
- RBC analysis is necessary to determine the percentage of type I (normal expression of GPI-anchored proteins), type II (partial deficiency), and type III (complete deficiency) RBCs

Depending on the markers assayed, flow cytometry for PNH can provide standard sensitivity (SS) or high sensitivity (HS)[3,22,23]

- SS assays are adequate for diagnosis of classic PNH but may miss patients with clone sizes <4%
- HS panels include ≥2 GPI-linked antibodies per lineage, one of which must be FLAER for WBC analysis and CD59 for RBC analysis

**Consider testing for PNH in patients with BMF disorders and persistent and unexplained cytopenia[8,26]**

FLAER, fluorescein-labeled proaerolysin; WBC, white blood cell.

# ASSESSMENT OF CLONE SIZE WITH FLOW CYTOMETRY IS IMPORTANT FOR PNH CLASSIFICATION[1,21,27]

| Category | Hemolysis | Treatment strategy | Typical clone size* |
|---|---|---|---|
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*PMN clone size.

# TESTS TO DIFFERENTIATE CLASSIC PNH FROM PNH/BMF[21,28]

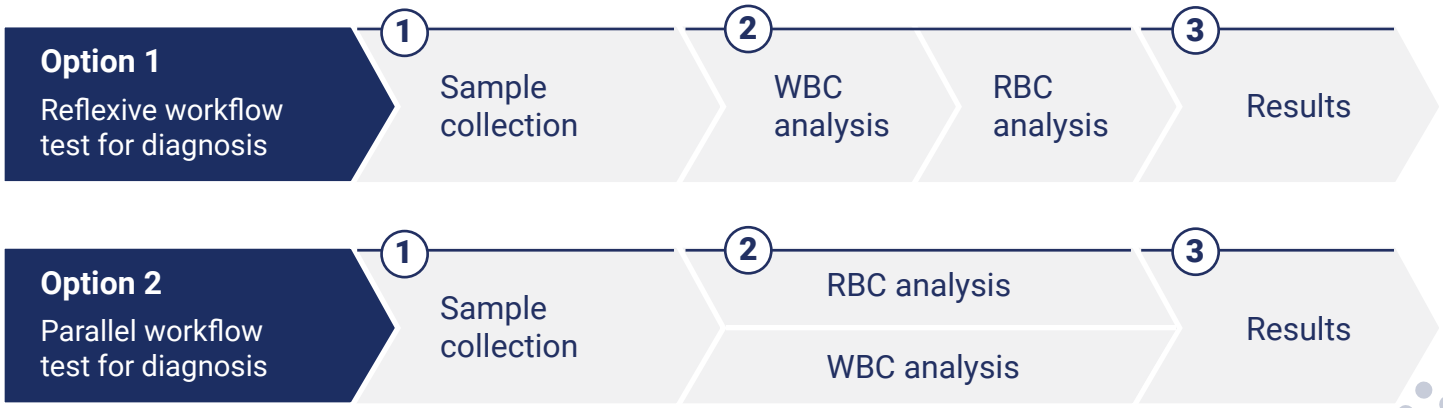
The following tests are performed to differentiate classic PNH from PNH associated with BMF:

Complete blood count and reticulocyte count for **bone marrow response**

Serum concentration of LDH, bilirubin, and haptoglobin for hemolysis

Bone marrow aspirate and biopsy for pathological characterization of PNH/BMF

# DETECTING GPI-DEFICIENT CELLS IN PNH[22,23]




[a]AA or low-risk MDS.
LDH, lactase dehydrogenase.

## 1 SAMPLE REQUIREMENTS[23,29-31]

**Draw 2-5 mL of peripheral blood**

**Use EDTA, heparin, or ACD tubes**

**Refrigerate after 24 hours**

**Test within 24-48 hours**

## 2 GUIDELINES FOR TESTING[22,23,29]

| | | 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<br>• 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]<br>• Monocytes: CD64, CD45, CD14,[a] and FLAER[b] |
| **Limit of detection[c]** | | 4% | 0.05% |

## MULTIPLE REFERENCE LABS OFFER FLOW CYTOMETRY TESTING TO CONFIRM PNH DIAGNOSES

| Laboratory | Sensitivity | Sample Information | Contact Information |
|---|---|---|---|
| **Labcorp**<br>Paroxysmal Nocturnal Hemoglobinuria (PNH)[30] | High | https://oncology.labcorp.com/tests/zzIO-295/pnh-evaluation | **1-800-447-5816**<br>LCOSpecCS@labcorp.com |
| **Quest Diagnostics**<br>PNH With FLAER (High Sensitivity)[32] | High | https://testdirectory.questdiagnostics.com/test/test-detail/94148/paroxysmal-nocturnal-hemoglobinuria-pnh-with-flaer-high-sensitivity?cc=MASTER | **1-866-697-8378**<br>https://www.questdiagnostics.com/contact-us |
| **NeoGenomics**<br>High Sensitivity PNH Evaluation[33] | High | https://neogenomics.com/test-menu/high-sensitivity-pnh-evaluation | **1-866-776-5907, option 3**<br>Client.Services@neogenomics.com |
| **CSI Laboratories**<br>PNH High-Sensitivity[34] | High | https://www.csilaboratories.com/flow/pnh-high-sensitivity/ | **1-800-459-1185**<br>clientservice@csilaboratories.com |

[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.
ACD, acid citrate dextrose; EDTA, ethylenediaminetetraacetic acid.

| Laboratory | Sensitivity | Sample Information | Contact Information |
|---|---|---|---|
| **Inform Diagnostics**[35] | High | https://www.informdx.com/wp-content/uploads/MLS-20-0100.4-Client-Resource-Guide.pdf | **1-855-856-0656**<br>https://www.informdx.com/contact-us/ |
| **ARUP**<br>PNH, High Sensitivity, RBC and WBC[36] | High | https://ltd.aruplab.com/Tests/Pub/2005006 | **1-800-522-2787**<br>clientservices@aruplab.com |
| **Dahl-Chase Diagnostic Services**[37,38]<br>Paroxysmal Nocturnal Hemoglobinuria Analysis | High | http://dahlchase.host4kb.com/article/AA-00231/15/ | **1-207-941-8200/1-800-660-1626**<br>cservice@dahlchase.com |
| **Hematogenix**[39] | High | NR | **1-708-444-0444**<br>ClientServices@hematogenix.com |
| **Mayo Clinic Laboratories**<br>PLINK[40,41] | High | https://www.mayocliniclabs.com/test-catalog/overview/62139#Specimen | **1-800-533-1710/ 1-507-266-5700**<br>mcl@mayo.edu |
| **Molecular Pathology Lab Network**<br>PNH – High Sensitivity by Flow[42,43] | High | https://www.mplnet.com/tests/paroxysmal-nocturnal-hemoglobinuria-1 | **1-865-380-9746**<br>services@mplnet.com |
| **BioReference Laboratories**<br>PNH by Flow Cytometry[31] | NR | https://www.bioreference.com/physicians/resources/test-directory/?type=by_test&test_id=5380 | **1-800-229-5227**<br>https://www.bioreference.com/contact/ |
| **PathGroup**<br>PNH Analysis (Flow Cytometry)[44] | High | https://pathconnect.pathgroup.com/testmenu/#/testinfo/UE5IRQ%3D%3D | **1-615-562-9300/1-888-474-5227**<br>http://www.pathgroup.com/company/contact/ |
| **Cleveland Clinic Laboratories**<br>High-Sensitivity Flow Cytometry for PNH[45] | High | https://clevelandcliniclabs.com/high-sensitivity-flow-cytometry-for-paroxysmal-nocturnal-hemoglobinuria/ | **1-800-628-6816/1-216-444-5755**<br>https://clevelandcliniclabs.com/contact-us/ |
| **Michigan Medicine Laboratories**<br>Flow Cytometric Immunophenotyping[46] | NR | https://mlabs.umich.edu/tests/pnh-marker-panel | **1-800-862-7284**<br>https://mlabs.umich.edu/form/contact |
| **University of Iowa Diagnostic Laboratories**<br>PNH Screening[47] | NR | https://www.healthcare.uiowa.edu/path_handbook/rhandbook/test1123.html | **Local: 1-319-384-7212**<br>**Toll-Free: 1-866-844-2522**<br>https://medicine.uiowa.edu/uidl/about-us |
| **UF Pathology Laboratories**<br>PNH – FLAER, Granulocytes/ Monocytes[48] | NR | https://pathlabs.ufl.edu/tests/test-directory-p/paroxysmal-nocturnal-hemoglobinuria-pnh-cd55-59-erythrocytes-flaer-granulocytes-monocytes/ | **Main: 1-352-265-9900**<br>**Jacksonville: 1-904-427-0865**<br>**Toll-Free: 1-888-375-5227**<br>https://pathlabs.ufl.edu/contact-us/ |
| **University of Pittsburgh Department of Pathology**<br>Clinical Flow Cytometry - PNH Evaluation[49] | NR | https://www.path.pitt.edu/divisions/section-laboratory-medicine/division-clinical-hematopathology/clinical-flow-cytometry-0 | **1-412-864-6173**<br>Rocher@upmc.edu |
| **University of Texas Medical Branch**<br>PNH, High Sensitivity, RBC and WBC[50] | High | https://www.utmb.edu/lsg2/Home/Details?id=1366 | **1-409-772-2222**<br>**1-800-917-8906**<br>https://www.utmb.edu/contact |
| **Oregon Health & Science University Lab Services**<br>PNH Test (High Sensitivity)[51] | High | https://www.ohsu.edu/lab-services/pnh-test-high-sensitivity | **1-503-494-8311**<br>https://www.ohsu.edu/about/contact-us |
| **UW Medicine Laboratory** Medicine and Pathology<br>PNH by Flow Cytometry[52] | NR | https://dlmp.uw.edu/test-guide/view/PNHFLO | **1-206-606-7060**<br>commserv@uw.edu |

The laboratories listed in the table above offer tests to identify PNH patients. Novartis does not have affiliations or relationships with these laboratories and does not endorse the use of any specific laboratory or test. This information is intended for reference only. There may be additional laboratories that conduct PNH testing. Conduct your own research and verify the capabilities and services of laboratories for your specific needs.

**Expected TATs for the above tests range from 1 to 7 days.[a]**

[a]Hematogenix, BioReference Laboratories, and PathGroup do not report the TAT of their PNH testing.
CPT, Current Procedural Terminology; NR, not reported; TAT, turnaround time.

## ③ GUIDELINES FOR REPORTING OF RESULTS[22]

### PNH reports should include:

**Clear, final interpretation**

- "PNH clone [present, absent] in [WBC, RBC, WBC and RBC]"
- Avoid the use of the terms "positive" or "negative"

**Reported clone sizes**

- WBC: total (neutrophils + monocytes) percentage clone size
- RBC: clone size; total percentage, type II percentage, and type III percentage

**Appropriate clone size terminology (WBC and RBC)**

- >1%: "PNH clone"
- 0.1%-1%: "minor PNH clone"
- <0.1%: "rare cells with PNH phenotype"

**All diagnostic and gating antibodies listed**

**Lower limit of quantification (%) indicated**

Both WBC and RBC assays

**Histograms or dot plots if possible**

**Retesting recommendations**

When "minor" or rare" clone populations are detected

## RECOMMENDATIONS FOR RETESTING AND MONITORING

### Patients should have their PNH clone size monitored at regular intervals using flow cytometry[29]

| | | |
|---|---|---|
| Changes in clone size may reflect a changing clinical picture and/or progression from subclinical to hemolytic PNH[29] | Patients with stable disease may be monitored annually; any change in clinical or hematologic parameters requires more frequent monitoring[29] | Patients with AA and/or "minor" PNH clones should be tested for clone size expansion every 3 to 6 months for the first 2 years and then annually thereafter if the clone size remains stable[22] |

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# SUMMARY

**Biomarker testing is essential to guiding therapeutic decisions**[3,7,8,21,27]

- The diverse presentation of PNH contributes to diagnostic delays[3,4]
- Timely and accurate diagnoses are critical for making appropriate treatment decisions for patients with PNH[3,7,8,21,27]
- Biomarker testing is a fundamental component of the diagnostic workup[3,6-8]
- Once suspected, PNH can be definitively diagnosed using flow cytometry[21]
- Multiple reference labs offer flow cytometry testing for PNH[30-52]
- For all of your patients, remember to **CHECK ThAT** and consider biomarker testing for PNH with flow cytometry

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