PRECISELY YOU

Not an actual patient.

Precision Medicine

BIOMARKER TESTING
and Its Role in PNH

Overview

Biomarker Testing and Routine Monitoring

Using Test Results

Learn More and Glossary

What Is PNH?[1,2]

- Paroxysmal nocturnal **hemoglobinuria** (PNH) is a rare **chronic** blood disease that causes an important part of your blood, **red blood cells (RBCs)**, to break apart unexpectedly. This breaking apart is called **hemolysis**
- It happens because your blood cells are missing **proteins** that protect them from a part of your body's immune system known as the **complement system**
- When your RBCs break apart, the **hemoglobin** inside them is released. Hemoglobin is the red part of RBCs. Its job is to carry oxygen around your body
  - The release of hemoglobin causes many PNH symptoms

To learn more about blood basics, please go to page 23

What Does PNH Mean?[1,2]

P Paroxysmal	N Nocturnal	H Hemoglobinuria
"Sudden and irregular"	"At night"	"Hemoglobin in urine" • This is the part that makes your urine look dark

- The original description of PNH was of hemoglobin in the urine occurring during the night. We now know that PNH symptoms can vary from person to person and hemolysis is a chronic part of the disease, occurring throughout the day even if you cannot see or feel it
  - PNH does not always cause dark urine, although many people with PNH may experience it at some point[1,3,4]

Who Can Be Diagnosed With PNH?[1-8]

PNH is an acquired, rare, life-long disease with symptoms that can vary from person to person[1,4-7]

It is estimated that

10 to 20

people per million

worldwide live with PNH[5]

Each year, roughly

500

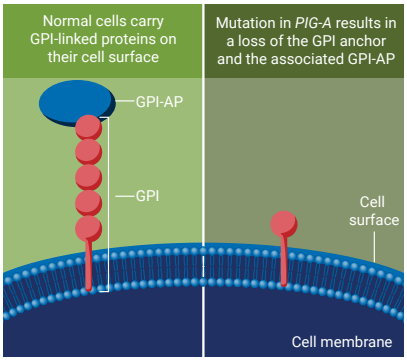
people in the United States

are diagnosed with PNH[2]

- PNH affects men and women equally, with a median age in the early to mid-30s at diagnosis[1,2,4,5,7]
- PNH is an **acquired** disease, which means you were not born with it, and it is not inherited, but rather, PNH develops in some people over time[1,8]
  - As a result, it cannot be passed on to your children

How Does PNH Affect Your Blood Cells?

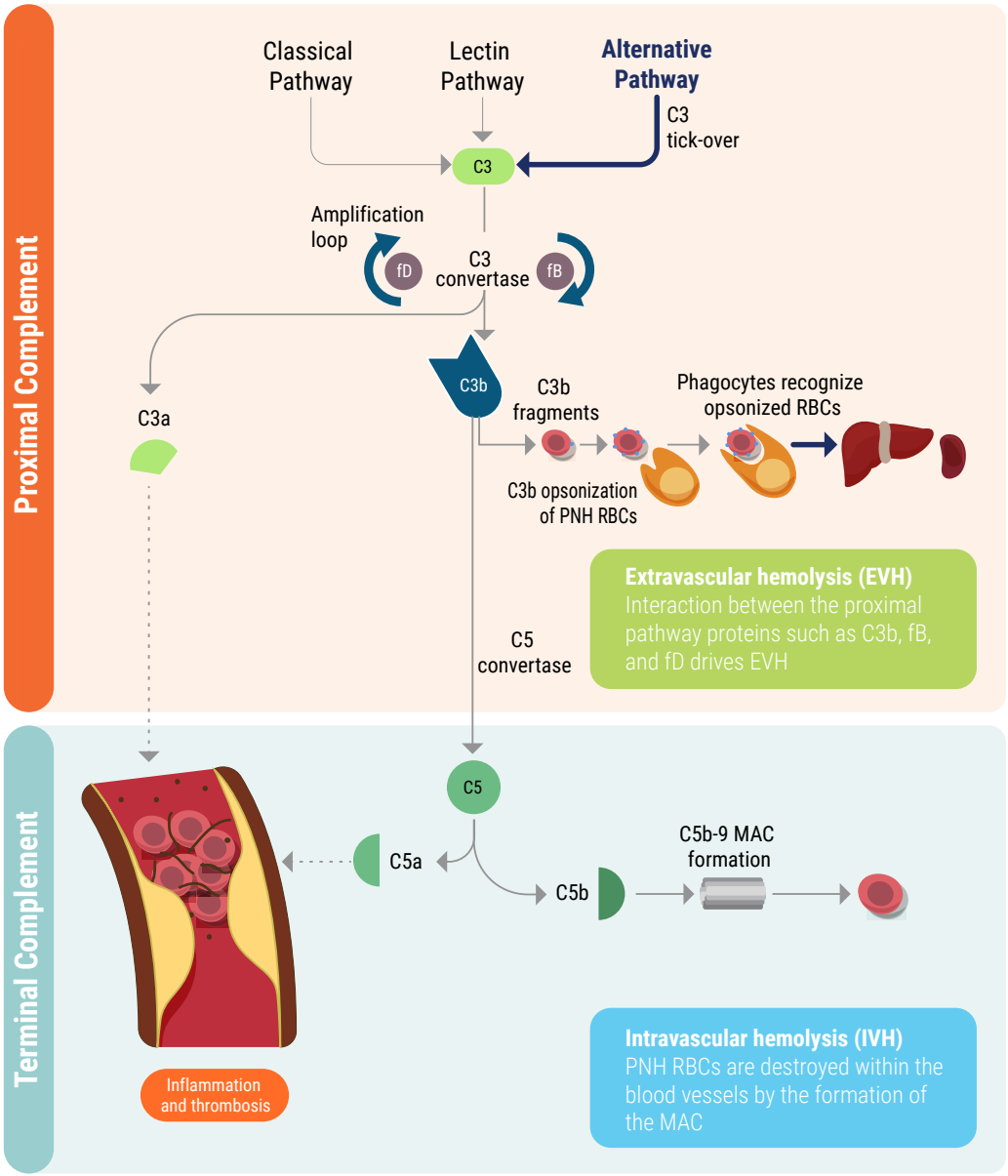
- Your **bone marrow**—a spongy tissue inside your bones—is where blood cells are made[2]
  - Normally, special cells inside your bone marrow (called hematopoietic stem cells) grow into healthy RBCs, **white blood cells (WBCs)**, and **platelets** in your body
- PNH happens because of a change (**mutation**) in the phosphatidylinositol glycan class A (*PIG-A*) gene of a single blood-forming stem cell in your bone marrow[1,8]
- The mutation in the *PIG-A* gene results in production of RBCs lacking protective proteins, CD55 and CD59, which help keep the complement system in check[1,8]



To learn more about what causes PNH, please go to page 22

GPI-AP, glycosylphosphatidylinositol-anchored proteins.

What Is the Complement System in PNH?[1,9-13]



C3, complement 3; fB, factor B; fD, factor D; C5, complement 5; MAC, membrane attack complex.

- The complement system involves a group of proteins in the blood. They help support the work of WBCs by fighting infections[1,2]
  - These proteins are always functioning at a very low rate, but when foreign or abnormal cells get into your body, these proteins are activated. They work to attack and destroy the abnormal cells in your body
- In PNH, since RBCs lack CD55 and CD59, the complement system is overactivated, leading to destruction of RBCs[1,14]
- There are 3 different pathways in the complement system: classical, lectin, and alternative. These can be divided into the upper (proximal) and lower (terminal) parts[1,9-13]
  - The upper part of the complement system leads into the lower part
  - Both the upper and lower parts of the alternative pathway play a role in contributing to hemolysis in PNH
- The upper part of the alternative pathway includes proteins such as factor B (fB), factor D (fD), and C3. Interactions between these proteins drive EVH[1,9-13]
- The lower part of the alternative pathway consists of interactions between C5 and other proteins, which drive IVH[1,9-13]

- Both types of hemolysis, IVH and EVH, contribute to PNH symptoms[1,9,15]

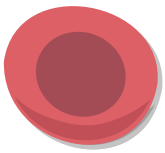
To learn more about treatment options, please go to page 20

What Leads to PNH?[1,2,8]

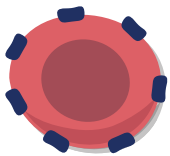
- An abnormal stem cell makes copies of itself. This leads to a population of stem cells that have a changed *PIG-A* gene. Doctors call this population of abnormal cells your "PNH clone"

- The abnormal stem cells turn into mature RBCs that have a changed *PIG-A* gene. These are called PNH RBCs

- The PNH RBCs lack proteins, CD55 and CD59, that protect normal RBCs from the complement system. This means PNH red cells may be attacked and destroyed by the complement system
  - PNH RBCs can have a partial or complete lack of GPI-APs (CD55 and CD59), making them vulnerable to attack



PNH RBC missing protective protiens



PNH RBC being attacked by complement

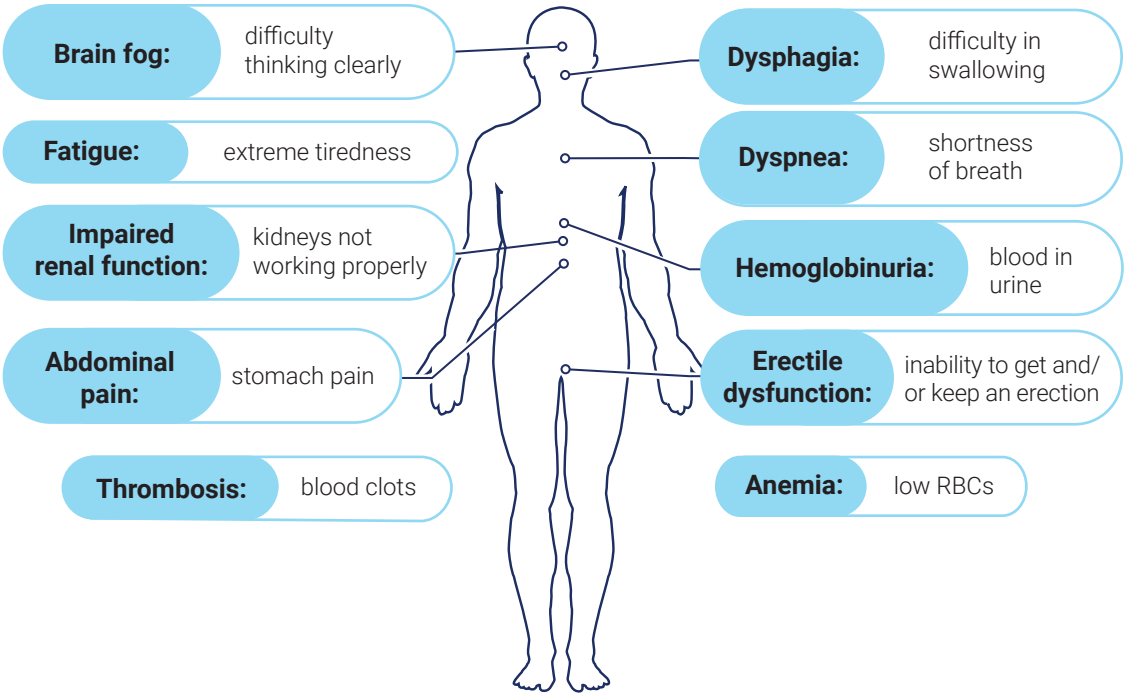
Destruction of the PNH RBC

- The destruction of PNH RBCs leads to hemolysis, the breakdown of RBCs[1,2,9]
  - There are 2 types of hemolysis:
    - **Intravascular hemolysis**, which happens in your blood vessels
    - **Extravascular hemolysis**, which happens most commonly in your liver and spleen

How Can PNH Affect You?[1,4,7]

- The symptoms of PNH can be very different from person to person
  - Some people have severe symptoms and others may have mild symptoms
  - You may get a new symptom at any point over the course of your disease
  - Other **bone marrow failure (BMF)** diseases, such as **aplastic anemia (AA)** and **myelodysplastic syndromes (MDS)**, may also be present in patients with PNH

Common signs and symptoms for PNH include[3,4,a]:



[a]This list does not include all possible symptoms associated with PNH.

- The course and impact of PNH may vary from person to person[1,6,7]
- Talk to your care team members about the symptoms you are feeling. Tracking your symptoms and changes in your lifestyle can help you and your care team find ways to manage your disease[1,6,7]

Notes

Notes (cont)

Biomarker Testing for PNH With Flow Cytometry

What Is Flow Cytometry? How Does It Work?

- Flow cytometry is a laboratory test used to diagnose and monitor PNH[7,16,17]
  - Flow cytometry tests detect the absence of proteins, including CD55 and CD59, which is the cause of PNH[7,16]
- Flow cytometry estimates the **PNH clone size**—the percentage of PNH cells that lack complement regulatory proteins in your blood[17,18]
  - PNH clone size relates to your symptom burden and **thrombosis** risk[19,20]
- Patients with PNH are typically classified by their clone size[1,5,21-23]
  - **Classic PNH** typically has clone sizes of >50%
  - Patients with an **overlapping BMF disorder*** have clone sizes <50%
  - Patients with **subclinical PNH** have clone sizes <10%
    - Subclinical PNH has no observable symptoms, with very low to no observed hemolysis

To learn more about different types of flow cytometry, please refer to page 23

*Other BMF diseases, such as AA and MDS, may also be present in patients with PNH.

How Can PNH Be Classified?[1,5,21-23]

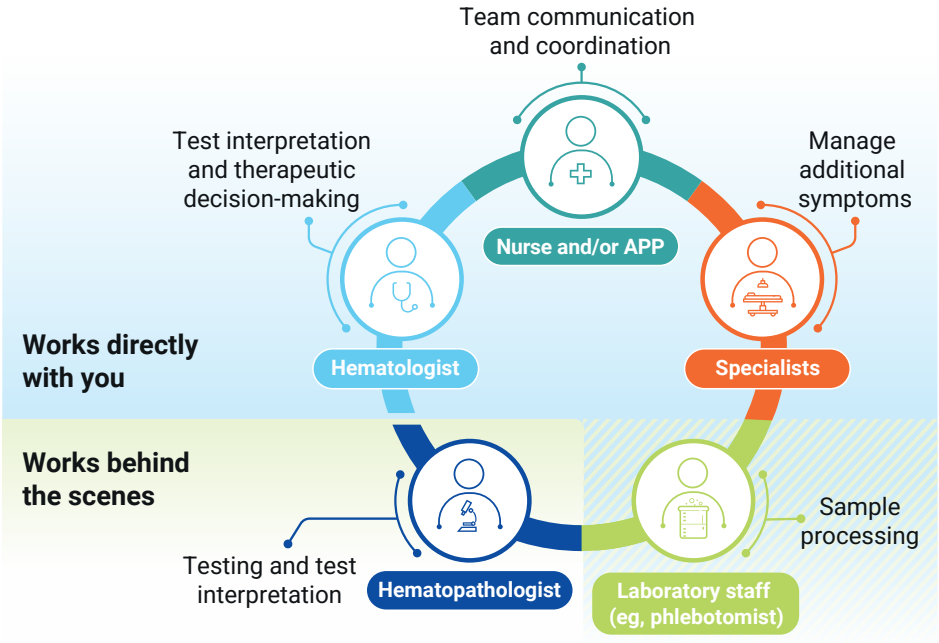
Category	Observed Hemolysis	Additional BMF Disorder	Treatment Strategy
Classic PNH	High	Absent	PNH-specific therapy
PNH with an overlapping BMF disorder	Low	Present	Treat underlying disease; patients with clinically significant hemolysis may benefit from PNH-specific therapy
Subclinical PNH	Very low or absent	Present	Treat underlying disease

To learn about your treatment options, please refer to page 20

- **Flow cytometry estimates the PNH clone size, which is important in determining your classification and treatment options**[17,18,21]
- **Flow cytometry is used to get your PNH diagnosis and can be used to monitor the PNH clone size**[7,11,16,17,24]
- **Your clone size may grow, so routine monitoring is crucial for your care**[7,11,16,17,24]

Who Is Involved in Biomarker Testing and Routine Monitoring?[7,25-29]

- Testing and monitoring require input from different specialties, so your care team can include a multidisciplinary team made up of health care professionals who specialize in different areas, such as **hematologists**, **advanced practice providers** (APP) (eg, **nurse practitioner**, **physician assistant**/**physician associate**), **hematopathologist**, **nurses**, **laboratory staff** (eg, **phlebotomist**), or other **specialists** for patients who may experience additional symptoms



- **Your care team will work together to provide you with the best care, even if you have never met them all**[7,27]
- **You may encounter additional individuals who can help support your PNH care**[7,27]

Questions to Ask Your Care Team After Diagnosis

If I have questions about PNH monitoring or flow cytometry, whom should I ask?

_____

_____

What is the most important thing you tell patients with PNH like me?

_____

_____

What PNH classification do I have?

_____

_____

What is the severity and/or prognosis of my PNH?

_____

_____

Do I have any other overlapping diseases related to my blood cells?

_____

_____

How might PNH affect my daily activities?

_____

_____

When do I start my treatment? What are my options?

_____

_____

What is the name of the therapy I will be receiving?

_____

_____

Routine Monitoring for PNH

Why Is Routine Monitoring Important?[2,7,16,24,30]

- Routine monitoring can be helpful in guiding your treatment because your clone size and symptoms can change over time, and breakthrough hemolysis may still occur

- **Because PNH is a chronic, life-long disease, routine monitoring is an important tool[6,7,24]**

When and What Should I Be Monitored for?

- To monitor your PNH, your care team will consider all your lab test results, signs, and symptoms, which may vary from person to person[1,7,16,24]
  - You may receive a bone marrow biopsy, which can help rule in or out other BMF diseases, such as AA[22,31]
  - However, flow cytometry is the standard test needed for diagnosing and monitoring PNH[7,11,16,17]
- Monitoring clone size with **high-sensitivity flow cytometry** at regular intervals can be valuable to help evaluate your PNH[7,16,17,24]
  - Your PNH clone size may be monitored every 6 months in the first 2 years, and then once a year if the disease is being treated and is stable
  - Testing for clone size changes if you have AA and/or “minor” subclinical PNH clones may be done every 3 to 6 months for the first 2 years, and then annually if the clone size remains stable
  - If your disease is stable, you may be monitored annually
  - Any change in your presentation may require more frequent monitoring
    - Changes in clone size may reflect a change in your clinical picture and/or progression from subclinical to classic PNH

- **Since PNH can manifest in various and serious ways, be sure to keep track of changes in your symptoms to discuss them with your care team[5-7]**

Signs and Symptoms to Track Can Include[3,4,*]:

General Signs and Symptoms	Pain	Fatigue
• Dark-colored urine • Shortness of breath • Difficulty swallowing • Erectile dysfunction • Brain fog	• Abdominal pain • Chest pain • Back pain	• Tiredness • Difficulty performing daily activities • Trouble concentrating • Weakness

Laboratory Tests[4,7,22,32]

- To routinely monitor your PNH, your care team might order some of these lab tests:
  - **Complete blood count (CBC)** to measure the amounts of different parts of your blood
  - Blood chemistry to measure the chemical balance of your blood
- Your care team may also use blood tests to look for high levels of:
  - A pigment called bilirubin, which can build up when your body destroys RBCs[9]
  - An enzyme called **lactate dehydrogenase (LDH)**, which increases with more destruction of RBCs
  - The amount of young RBCs in your bone marrow called reticulocytes. This is usually high if you are experiencing destruction of RBCs

To learn more about blood and lab basics, please refer to page 23 and 24

*This list does not include all possible symptoms associated with PNH.

- **It is important for you to keep track of your lab results and discuss any changes with your care team**[7,16]

PNH Lab Tracker[21,33,34]

Use this form to record your lab values and visits, and bring it with you to each appointment

		Tests Results					
Laboratory Tests	**Reference Values**[a]	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**	**Date:**
Hemoglobin	Male: 13.0-18.0 g/dL Female: 12.0-16.0 g/dL						
Platelets	150,000-450,000/µL						
ARC	25,000-100,000/µL						
Leukocytes	4000-11,000/µL						
Total bilirubin	0.3-1.0 mg/dL						
LDH	80-225 U/L						
Haptoglobin	83-267 mg/dL						
PNH clone size	%						

Your care team may use some or all these tests, in addition to others, to monitor your health. **Talk to your care team to learn more about your PNH management plan.**[7]

To learn more about how your lab values can be affected by PNH, please refer to page 24

ARC, absolute reticulocyte count.

[a]Reference values may differ based on laboratories; values are provided as examples. Please confirm individual reference values with the laboratory your care team uses. Interpretation of test results in relation to the reference range(s) may depend on your clinical picture and is at the discretion of your care team.

Blood Transfusion Record[5,24,b]

Use this form to keep track of your blood transfusions, if applicable, as part of your PNH treatment

		Hemoglobin Level	
Date	Units	Before	After

How many blood transfusions did you have each month?

January: _____

February: _____

March: _____

April: _____

May: _____

June: _____

July: _____

August: _____

September: _____

October: _____

November: _____

December: _____

[b]Not every patient will receive blood transfusions. Blood transfusions may have the potential for complications, such as iron overload, so tracking your transfusions can be helpful.

Questions to Ask Your Care Team During Monitoring and Management

What are your goals for managing my PNH? What does successful management look like?

_____

_____

Are there additional steps to take if management goals are not reached?

_____

_____

How will you measure whether my condition is getting better or worse?

_____

_____

What are some lab tests you would order to help track my PNH and how often do I need to get them?

_____

_____

What are my flow cytometry test results and what do these results mean?

_____

_____

Which of the test results should I focus on?

_____

_____

How will you or I know if my treatment plan needs to be changed?

_____

_____

What is the next plan if treatment does not work for me?

_____

_____

What are the potential treatment side effects?

_____

_____

How will you help manage my symptoms or any side effects of my treatment?

_____

_____

Can I have my regular monitoring tests done earlier than scheduled if I am experiencing symptoms?

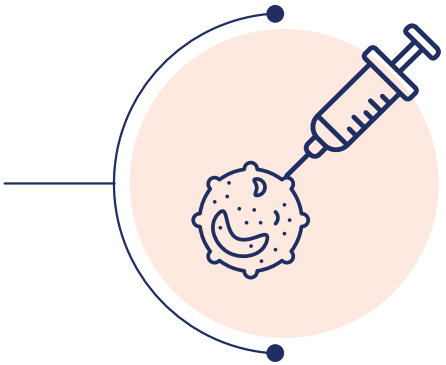
_____

_____

- **Everyone's experience with the disease can be unique. No single sign, symptom, or lab result defines PNH**[1,7]
- **See your care team regularly. Routine monitoring is important for understanding your disease and determining what treatment options are right for you**[7]

What Treatment Options Will Be Available to Me? What Else Should I Know About PNH Treatments?

- Because PNH is considered a chronic disease, meaning it lasts for a long time, the only known cure is a bone marrow transplant[1,6,7]
- Your care team will use your flow cytometry test results and routine monitoring to determine if you are a good candidate for a particular approved therapy for PNH[7,11,21,24]
  - Your treatment can vary based on your PNH classification and clinical picture, including signs, symptoms, and lab values
- Additional supportive therapies, like blood transfusions and iron supplementation, may also be helpful for patients with PNH experiencing **anemia**[5,7,22]
- Your health care professional or a member of your care team may talk to you about potential safety programs required for you to participate in, depending on the PNH therapy that has been selected together with your care team[35-37]
- Complement system inhibitors carry a risk of infections from **encapsulated bacteria**. Treatments approved for PNH affect parts of the complement system, which is a part of your immune system, and can lower your body's ability to fight infections[11,31,38]
  - As a result, your health care professional or a member of your care team may discuss vaccine requirements needed to receive the PNH therapy that has been selected together with your care team



- **Because PNH is a chronic disease, it is important that you take your therapy as prescribed, even if you are feeling better**[1,6,7]

Notes (cont)

Learn More

Are There Any Additional Resources I Should Know About?

There are multiple online resources full of information and support for patients like you. Some resources are listed below.

AA·MDS INTERNATIONAL FOUNDATION	The Aplastic Anemia and MDS International Foundation (AAMDSIF) at: **https://www.aamds.org/**[39,40]	AAMDSIF is the world's leading nonprofit health organization dedicated to providing support, education, community, and research for patients, families, and health professionals impacted by AA, MDS, PNH, and related bone marrow failure diseases
NORD®	National Organization for Rare Disorders (NORD) at: **https://rarediseases.org/**[41]	A nonprofit patient advocacy organization dedicated to helping patients and their families with rare disorders, including PNH
PNH GLOBAL ALLIANCE	PNH Global Alliance at: **https://pnhglobalalliance.org**[42]	An alliance of global organizations for patients with PNH created to share information and expertise, collaborate on common challenges and issues, and leverage their combined voices for the benefit of the PNH community

This list of resources is not exhaustive. The above websites are independently operated and not managed by Novartis Pharmaceuticals Corporation. Novartis assumes no responsibility for the content on the sites.

Diagnosing and monitoring PNH can be complex. This section will help you understand some of the science behind it and provide you with additional information.

Understanding the Cause and Diagnosis of PNH

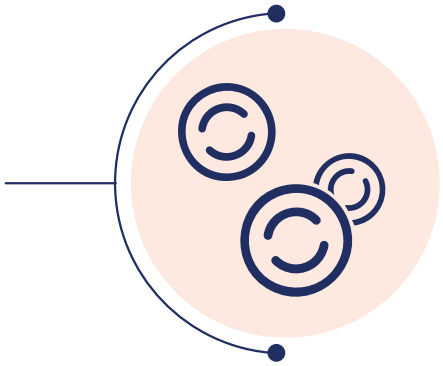
PNH is caused by a change (mutation) in the phosphatidylinositol glycan class A (*PIG-A*) gene of a single blood-forming stem cell in your bone marrow, resulting in the loss of GPI-AP on the RBC surface[1,8]

- The complement regulatory proteins CD59 and CD55 are GPI-anchored proteins and among those proteins that are lost in patients with PNH
- The lack of these proteins exposes RBCs to attack by part of your body's immune system: your complement system

- There are 2 types of flow cytometry tests used to diagnose PNH: low sensitivity and high sensitivity[7]
  - Low-sensitivity flow cytometry can be used to diagnose PNH[7]
  - High-sensitivity flow cytometry is able to detect smaller PNH clones in patients compared with low-sensitivity flow cytometry. This allows high-sensitivity flow cytometry to be used in diagnosis and monitoring of PNH[7,16,17]
    - This type of flow cytometry analyzes both your RBCs and WBCs[17,21]
    - RBC analysis determines the amount of missing regulatory proteins and PNH type, whereas WBC analysis can more accurately determine your clone size[17,21]

Blood Basics

- To better understand PNH, it helps to know a little bit about the different types of blood cells you have and how your body makes blood cells
- Your blood carries 3 different kinds of blood cells. Each one has an important role to play[2,32]
  - RBCs carry oxygen from your lungs to all the cells in your body
  - WBCs are cells of the immune system that protect you by attacking infectious disease and foreign invaders. There are many different types of WBCs
  - Platelets help your blood clot and control or stop bleeding



Lab Basics[5,7,24,32]

- In addition to your PNH clone size, your care team may use several different tests to monitor and track your PNH over time. The results from these tests will help your care team better manage your PNH

Lab	What Does It Do? How Can PNH Affect It?
Hemoglobin	Carries oxygen to your body tissues. This is likely reduced in patients with PNH
LDH	An enzyme released from RBCs when they are destroyed by hemolysis. The level of LDH in the blood can show how much hemolysis is happening
Haptoglobin	A substance normally found in your blood. Haptoglobin attaches to free hemoglobin in your blood and takes it to the liver to be recycled. When there is hemolysis, the free hemoglobin rises and the haptoglobin level falls, so low haptoglobin shows that hemolysis is happening
Total bilirubin	Bilirubin is a yellowish pigment found in bile, a fluid made by the liver. It is a waste product produced by the breakdown of RBCs and can be increased in a patient with PNH experiencing hemolysis
ARC	The number of reticulocytes, which are immature RBCs that have recently moved from the bone marrow into circulation, in a volume of blood. Patients with PNH may have an elevated reticulocyte count because the bone marrow is producing a lot of new RBCs to replace those that are destroyed through hemolysis

Glossary

Acquired: Not inherited, or present at birth, but developing after birth[1,8]

Anemia: The condition of having a lower-than-normal number of RBCs or quantity of hemoglobin. Anemia diminishes the capacity of the blood to carry oxygen[32]

Aplastic anemia: Anemia that results from the failure of the bone marrow to produce enough blood cells[32]

Bone marrow: The soft tissue inside most bones. It works to create the cells in your blood: RBCs, WBCs, and platelets[32]

Bone marrow failure: Severe dysfunction of the blood cell–producing bone marrow, resulting in low levels of RBCs, WBCs, and platelets[43]

Chronic disease: A disease lasting for a long time. It can usually be controlled but not cured[32]

Complement system: Also known as the complement cascade; in healthy individuals, a sequence of protein reactions in the blood that is part of the body's natural defense system. It helps fight against bacteria and other foreign matter in the body[1]

Complete blood count: A lab test that measures and evaluates several components and features of your blood and detects a wide range of disorders[32]

Encapsulated bacteria: Bacteria, protected by a surrounding layer (capsule), that can cause serious infections if not recognized and treated early[11,31,32,39]

Extravascular hemolysis: "Extra" means outside and "vascular" means blood vessels. Extravascular hemolysis is when RBCs break down outside of the blood vessels[1,32]

Fatigue: Tiredness, trouble concentrating, and weakness to the point where even normal, everyday activities become a struggle[32]

Hemoglobin: Protein that is found inside RBCs that carries oxygen. When it is released into the bloodstream during hemolysis, it becomes free hemoglobin. Free hemoglobin is harmful and can lead to serious health problems[2,32]

Hemoglobinuria: Hemoglobin in the urine. Some patients with PNH may have it at diagnosis, but many will experience it at some time. Because of the reddish-brown color of hemoglobin, it results in dark, sometimes "cola-colored" urine[1,2,4,5,13]

Hemolysis: The destruction of RBCs by the body's natural defense system. Hemolysis is the main cause of the signs, symptoms, and serious health problems in PNH, including some that are life-threatening[1,15,32]

High-sensitivity flow cytometry: The gold standard test for confirming whether or not you have PNH. It counts the actual number of RBCs and WBCs affected by PNH in a small blood sample. The results indicate your clone size[7,17]

Intravascular hemolysis: "Intra" means inside and "vascular" refers to blood vessels. Intravascular hemolysis is when RBCs break apart or burst while they're still inside the blood vessels[1,32]

Lactate dehydrogenase (LDH): An enzyme found in RBCs that is released during hemolysis. Testing for LDH can help show how much hemolysis is happening in your body[24,32]

Leukocyte: A type of of blood cell that is made in the bone marrow and found in the blood and tissue. Leukocytes are part of the body's immune system and help the body fight infection and other diseases[32]

Mutation: Any change in the DNA sequence of a cell[32]

Myelodysplastic syndromes (MDS): A condition in which there's a problem with the way bone marrow makes blood cells. A small percentage of patients with PNH also have MDS[7,19,32]

Platelet: A part of blood cells that helps form blood clots to slow or stop bleeding and help wounds heal[32]

PNH clone size: The percentage of blood cells in your body affected by PNH[17,18]

Proteins: Molecules inside your body that are needed to help it function properly[32]

Red blood cells (RBCs): A type of cell found in your blood that delivers oxygen and removes waste (carbon dioxide) in your body. RBCs affected by PNH are attacked and destroyed because they are missing protective proteins[1,32]

Thrombosis: The formation of blood clots when parts of your blood clump together. In a healthy body, this can stop bleeding when you're cut or injured. But in certain conditions, these clumps can block blood flow in the veins and arteries, which can be dangerous. In PNH, thrombosis can happen at any time and can cause serious health problems[1,32]

White blood cells (WBCs): A type of cell found in your blood that helps your immune system fight disease and infection[32]

References

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Summary

As we've seen, diagnosis, monitoring, and management of PNH are complex processes that require several steps and collaboration between you and your care team

Understanding the purposes of flow cytometry, routine monitoring, and knowing the right questions to ask may help you and your care team achieve the best possible health outcomes

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