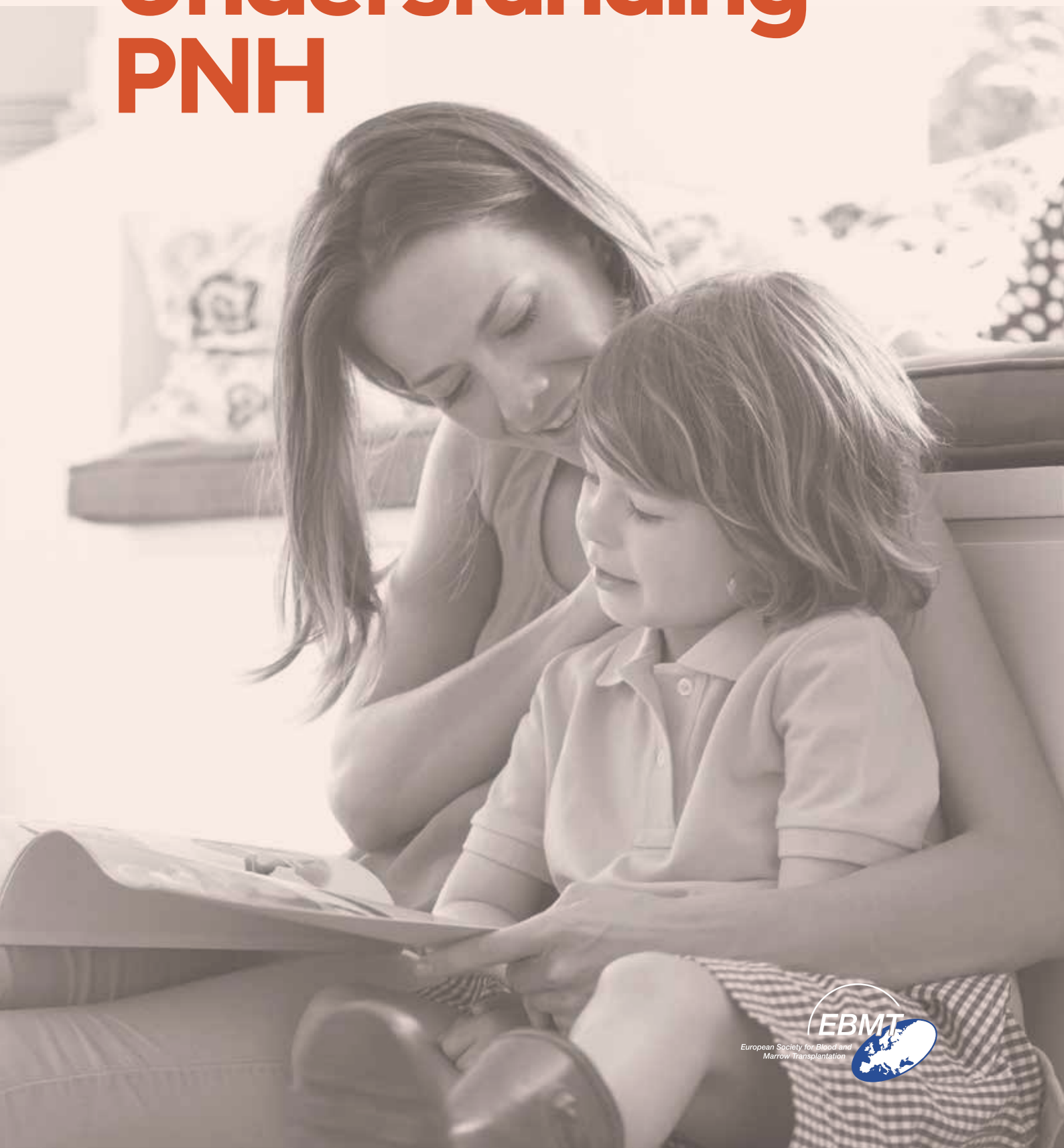
PNH

Brochure and diary for patients

Understanding PNH



EBMT
European Society for Blood and Marrow Transplantation

The Nurses Group of the European Society for Blood and Marrow Transplantation (EBMT NG) gratefully acknowledges the following individuals for their critical review and contributions to this brochure:

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Contributors would like to extend a special thanks to Lars Ritzal, Germany, for his invaluable input to this brochure from the perspective of a patient with PNH.

This brochure has been designed for patients with paroxysmal nocturnal haemoglobinuria (PNH) and their carers, family and friends. It contains information about PNH, including causes, symptoms and management options, as well as lifestyle tips to help make day-to-day life easier.

The symptom diary found at the rear of this brochure can be used by people diagnosed with PNH to keep a log of their symptoms and to record how their treatment is making them feel. Discussing the diary entries at each appointment will help both the doctor and other members of the healthcare team to keep track of symptoms and changes, which will aid in determining if modifications to treatment are required.

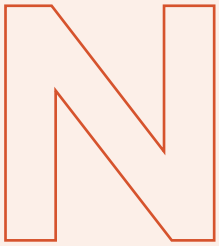
Terms that have been underlined are defined in the Glossary at the end of the brochure.

What is PNH?

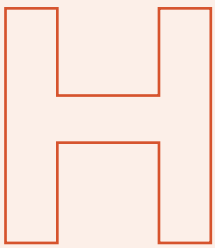
PNH is a very rare and complex disease. People with PNH may experience a range of symptoms. Some people experience virtually no symptoms, whereas others may have various symptoms and complications.

PNH was given its name based on several key features of the disease. Explanations of the medical terms within the name are given in the figure below:

Paroxysmal means occurring in episodes. PNH is actually a disease where the destruction of blood cells is ongoing all the time. However, there are times when the rate of destruction may be increased and the symptoms experienced get worse.



Nocturnal means occurring in the night. The dark urine (haemoglobinuria) that can occur in PNH tends to be most noticeable in the morning so it was originally thought that the destruction of red blood cells was occurring at night time. We now know it occurs throughout the day as well.



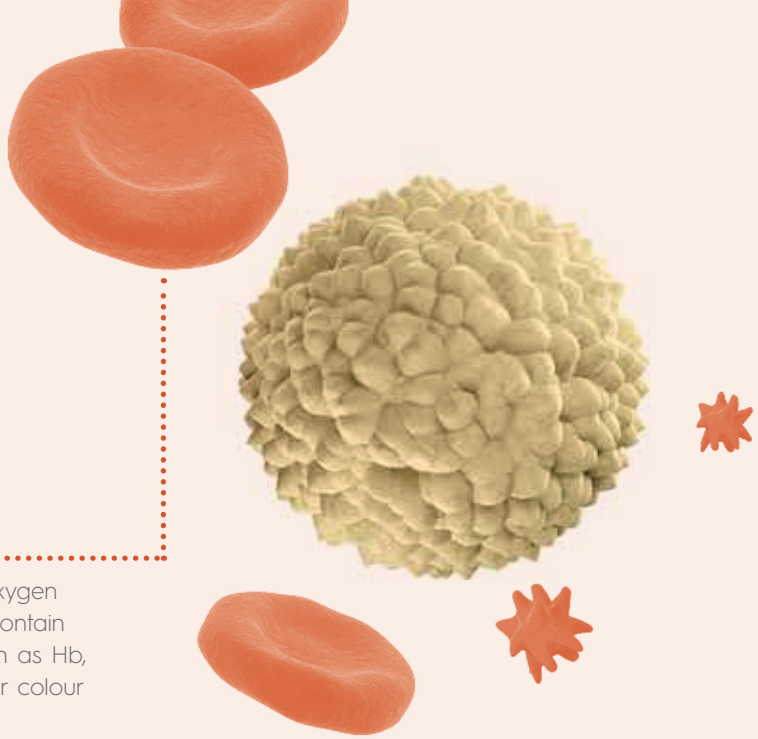
Haemoglobinuria means haemoglobin presence in the urine. In PNH, when red blood cells are destroyed the haemoglobin may be released into the urine which makes the urine appear a dark colour. However, only about 1 in 4 people have this symptom when they are diagnosed with PNH and others may never experience it.

Now that PNH is better understood, we know that its name does not describe the experiences of all patients and does not completely reflect the nature of the disease.

About blood

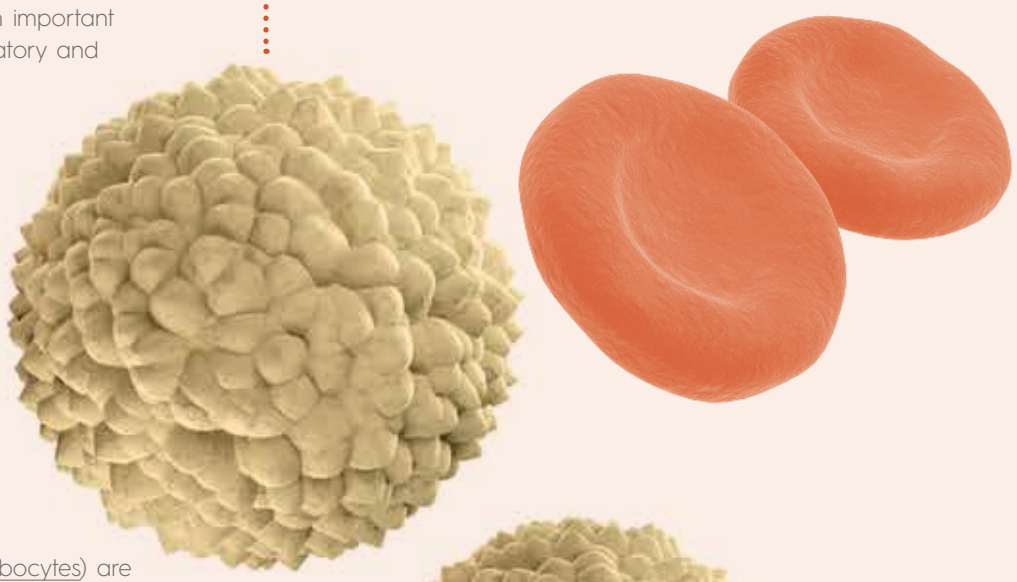
Blood is constantly circulated around the body by the pumping action of the heart, delivering nutrients to cells and removing waste. Approximately half of the blood in our bodies is made of liquid called plasma; the other half is made up of cells.

Blood cells are cells that are produced in the bone marrow and fall into three types; red blood cells, white blood cells and platelets.

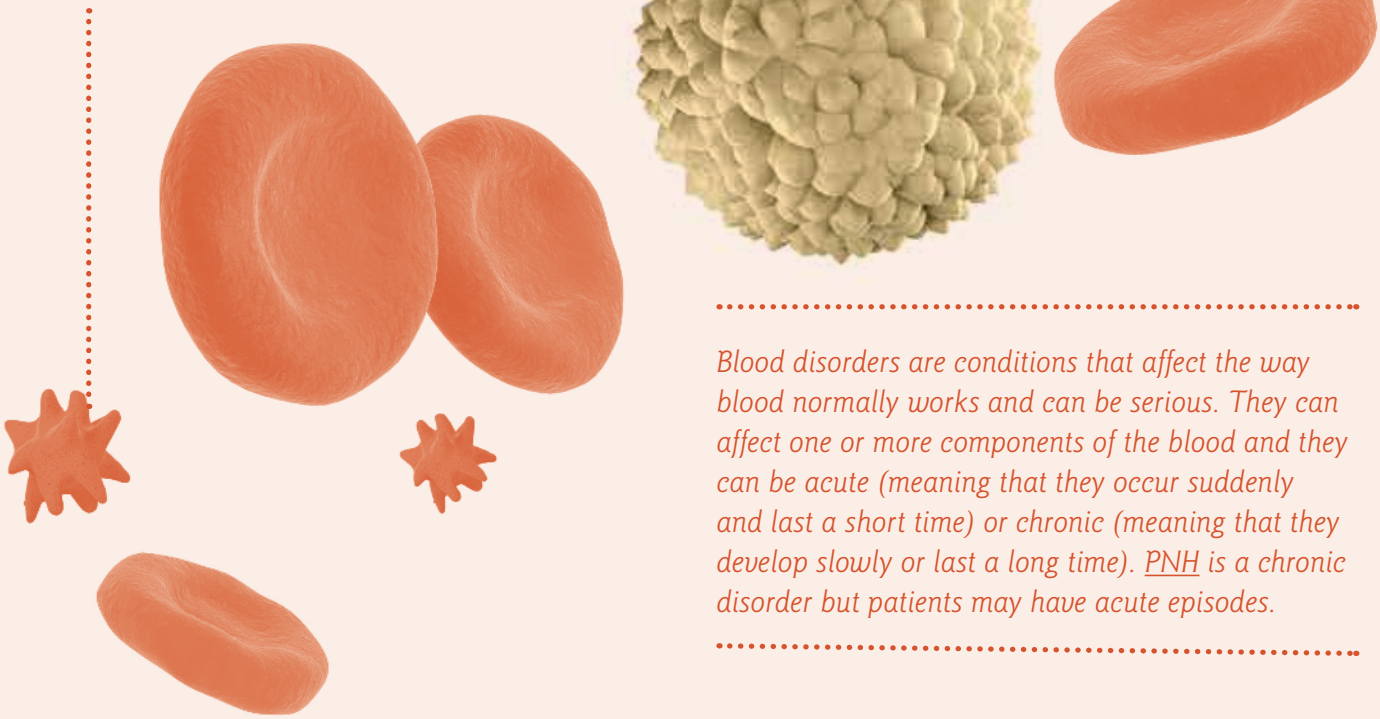


Red blood cells (erythrocytes) circulate oxygen around the body. They contain haemoglobin, also known as Hb, which gives red cells their colour

White blood cells (leukocytes) play an important role in the inflammatory and immune responses



Platelets (thrombocytes) are involved in the initial stages of the blood clotting process and stop bleeding



Blood disorders are conditions that affect the way blood normally works and can be serious. They can affect one or more components of the blood and they can be acute (meaning that they occur suddenly and last a short time) or chronic (meaning that they develop slowly or last a long time). PNH is a chronic disorder but patients may have acute episodes.

Who is affected by PNH?

PNH is a very rare disease; it only affects around 16 people in every million and there are only 1.3 new cases diagnosed per million people each year. It is an acquired genetic disease, which means that it is not an inherited disorder and it cannot be passed down to children from their parents. It is not contagious. Men and women are equally affected by PNH and, although it can occur in all age groups (including children), it is most frequently diagnosed in people in their early- to mid-30s, often following subtle symptoms that can develop and get worse over a long period of time.

PNH is often associated with conditions that cause the bone marrow to not function as well as normal such as aplastic anaemia (AA). People with bone marrow failure syndromes are more likely to develop PNH.

What causes PNH?

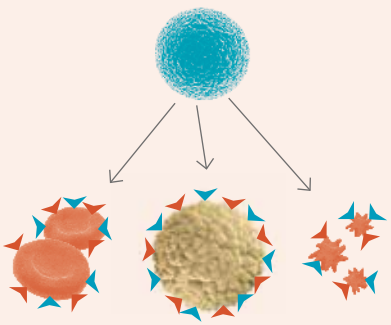
The complement system is a part of the body's immune defence system, which works to attack and destroy bacteria, viruses and abnormal cells. Normal blood cells have protective proteins on their surface, which are there to defend cells from attack by the complement system. These proteins are attached to the cell surface by a different group of proteins (GPI-anchor proteins) made by the PIG-A gene. In PNH, usually a change (mutation) in the PIG-A gene within the bone marrow stem cells means that some blood cells have fewer or a complete absence of GPI-anchor proteins on their surface. This, in turn, means that they have fewer or no protective proteins attached to them, and so cannot protect themselves from the complement system. The PIG-A gene mutation can affect red blood cells, white blood cells and platelets. Affected red blood cells are easily broken down by the complement system (a process called haemolysis), whilst affected white blood cells and platelets are activated by the complement system. The extent to which each type of cell is affected may vary. This is described as type I, type II and type III and is shown in the figure below.

It is not fully understood why the PIG-A gene mutation occurs, although there is a link with other forms of bone marrow failure such as AA or myelodysplastic syndrome (MDS). This relationship does not relate to all patients, however, and some may have PNH without any other form of bone marrow failure or 'classical PNH' as it is sometimes described.

Types of PNH cell

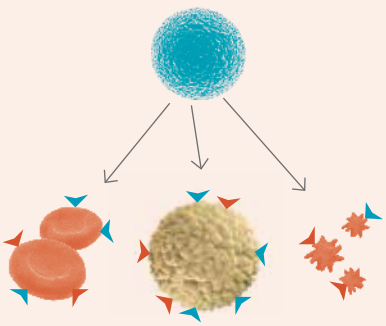
The blood cells of people with PNH are divided into three types:

Normal (type I) stem cell



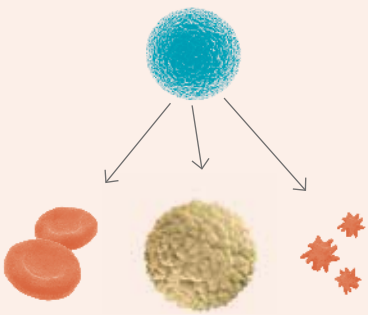
PNH I cells (also known as type I cells) are normal blood cells that have the proteins on their surface to protect them from destruction or activation by the complement system

PNH (type II) stem cell



PNH II cells (also known as type II cells) are missing some of the protective proteins from their surface so are partially sensitive to destruction or activation by the complement system

PNH (type III) stem cell



PNH III cells (also known as type III cells) are missing all of the protective proteins from their surface so are easily destroyed or activated by the complement system

Doctors use a type of test called flow cytometry to measure the percentages of the different types of blood cells. More information on flow cytometry is provided in Section 6: How is PNH diagnosed and monitored?

PNH clone size

The so-called PNH clone size refers to the proportion of PNH cells without normal expression of GPI-anchor proteins (PNH II cells and PNH III cells) versus normal cells (PNH I cells). For example, a person with 60% blood cells without GPI-anchor proteins and 40% normal cells has a PNH clone size of 60%. In general, the doctor or nurse will be referring to the white blood cell or 'granulocytic' clone when they discuss PNH clone size. This is because white blood cells are not destroyed by the complement system and are therefore more stable to measure than red blood cells, which are vulnerable to depletion or may be present due to a blood transfusion and are therefore not produced by the patient's own bone marrow.

The proportion of PNH clone cells can vary enormously, with some people having very few PNH cells and others having almost 100% PNH cells. Furthermore, the PNH clone size can change over time and should be checked regularly as it can help give a better understanding about the disease. It is not uncommon for the PNH clone size to increase after treatment (for example with drugs such as antilymphocyte globulin [ALG] or antithymocyte globulin [ATG]).

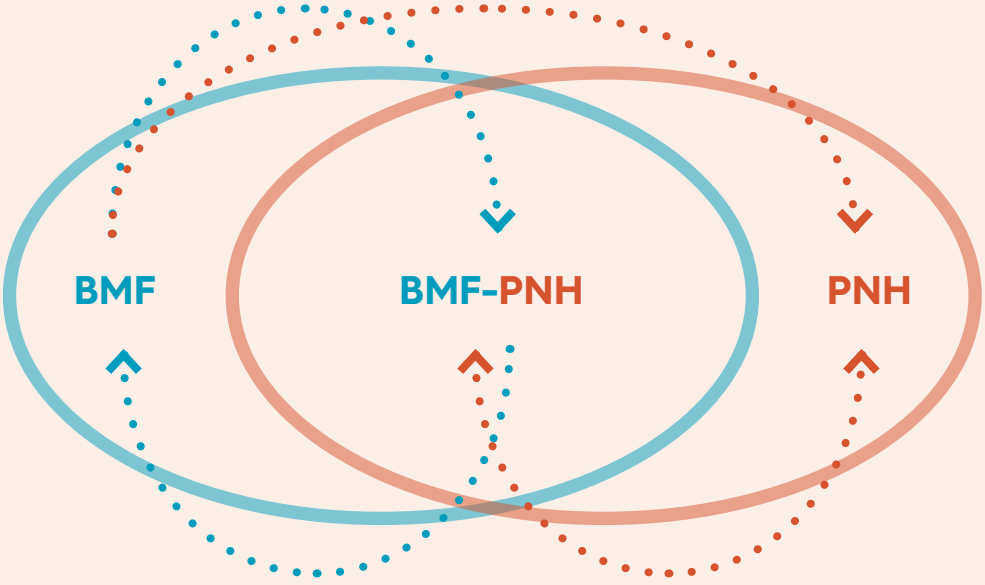
PNH is a disease in which PNH type II and III red blood cells are destroyed, and PNH type II and III white blood cells and platelets are activated because they lack protective proteins on their surface.

Bone marrow failure

The exact reason why some people develop PNH is not known; however, PNH often occurs alongside other conditions that make the bone marrow less effective at producing new blood cells, such as AA and MDS.

Currently, the causes of bone marrow failure underlying PNH are poorly understood. However, it is important to note that bone marrow failure can develop over time and PNH can still develop in patients who have previously been cured of a bone marrow failure condition. Therefore, it is important to keep a track of changes in blood count and/or symptoms to monitor bone marrow function.

Relationship between bone marrow failure and PNH



What are the signs and symptoms of PNH?

The signs and symptoms of PNH are varied and some people will feel well despite having PNH whilst others can be very unwell, with complications that can be life-threatening. PNH can often be undiagnosed for years because it presents differently in each person and it has a variety of symptoms usually associated with other conditions.

It is very difficult to predict how PNH will affect different people and how the disease might change over time. People who have a disease of the bone marrow, such as AA, may have PNH diagnosed in a routine screening test for PNH, even if they have no symptoms of PNH.

Listed below are the signs and symptoms that a person with PNH may experience. It is important to remember that some people may have very few problems and may not experience all of these signs and symptoms. More information on these signs and symptoms and other consequences of PNH is provided on the next page.

01 — Thrombosis
02 — Haemolysis
03 — Anaemia
04 — Fatigue
05 — Pulmonary hypertension (PHT) and dyspnoea
06 — Arterial hypertension (AHT)
07 — Jaundice
08 — Gallstones
09 — Abdominal pain and difficulty swallowing
10 — Renal dysfunction and chronic kidney disease
11 — Erectile dysfunction

The following symptoms can occur throughout the body

Thrombosis

Thrombosis is the formation of blood clots within blood vessels. Blood is normally able to form clots at times of damage, such as when there is an injury. However, in PNH the blood is able to form clots too easily. This is a serious condition because blood clots can cause obstruction to blood flow and stop oxygen getting to the body's tissues. The obstruction of a vein or artery by a blood clot from another site is called a thromboembolism. This can be very serious or even fatal depending on the location of the blocked blood vessel, and may lead to a heart attack, stroke or organ damage. PNH can also cause thrombosis in unusual veins such as the hepatic veins draining the liver (Budd-Chiari Syndrome). Thromboembolism is the leading cause of death in people with PNH.

Haemolysis

Haemolysis is the destruction of red blood cells. This releases haemoglobin into the plasma causing symptoms such as darkened urine and anaemia. In severe haemolysis, the destruction of red blood cells causes a quicker release of haemoglobin into the bloodstream and may cause excessive tiredness, shortness of breath and a higher heart rate. Free haemoglobin also binds to nitric oxide, creating a lack of nitric oxide in the blood. This lack of nitric oxide causes spasms in certain muscles of the body, such as the abdomen and the oesophagus (which connects the mouth to the stomach), resulting in high levels of pain and an increased risk of thromboembolism. The same process may cause swallowing difficulties or erectile dysfunction.

Anaemia

Anaemia is defined as a decrease in the amount of red blood cells in the blood. Low red blood cell counts can occur due to a reduced production of red blood cells resulting from poor bone marrow function, or due to an increased destruction of red blood cells (haemolysis). One of the primary characteristics of PNH is haemolytic anaemia. People with anaemia may experience tiredness (fatigue), shortness of breath especially upon exertion (e.g. when climbing stairs) or on relaxation, pallor (pale colour of skin), palpitations (awareness of their own heartbeat), dizziness and fainting. A person's haemoglobin level may not reflect the levels of fatigue or impairment to quality of life they experience.

Fatigue

Fatigue is a symptom of anaemia, but fatigue can also occur independently of anaemia. In PNH, the tiredness experienced by a person is often much worse than would be expected in people with other types of anaemia. One explanation for this may be the reduced levels of nitric oxide. Excessive tiredness can be debilitating, affecting work life, home life and the ability to do normal everyday activities. People with PNH may have to adapt their lives and activities because of this tiredness. Sometimes excessive tiredness may be misdiagnosed as depression.

Pulmonary hypertension (PHT) and dyspnoea

Pulmonary hypertension (PHT) is a condition in which the blood pressure of the arteries of the lungs is abnormally high. Nearly half of people with PNH have evidence of PHT. As PHT affects the lungs, shortness of breath and difficulty in breathing (dyspnoea) are common symptoms of this condition, which can also put extra strain on the heart. Severe fatigue and severe dyspnoea are two symptoms of PNH that are consistent with PHT. PHT is also associated with an increased risk of other serious health problems, such as thrombotic events (TEs), and may be a very serious condition if left unaddressed.

Arterial hypertension (AHT)

Arterial hypertension (meaning high blood pressure) is a medical condition in which the blood pressure in the arteries is elevated. Some patients report headaches, light-headedness, vertigo (when a person feels as though they are moving or spinning when they are not), tinnitus (the perception of sound in the absence of any corresponding external sound) or altered vision. Usually hypertension does not cause symptoms initially, but sustained hypertension over time is a major risk factor for hypertensive heart disease, coronary artery disease, stroke, aortic aneurysm, peripheral artery disease and chronic kidney disease.

Jaundice

Bilirubin is the yellow pigment released from the breakdown of red blood cells, and this pigment can cause jaundice (yellow discolouration of the eyes or skin) at times of significant haemolysis (destruction of red blood cells). Jaundice may also be accompanied by itchy skin.

Gallstones

Gallstones are hardened deposits of digestive fluid that can form in the gall bladder, an organ that processes bile within the gut. If gallstones cause a blockage in the bile duct, they may result in sudden, worsening pain in the abdomen, nausea, back pain between the shoulder blades or pain in the right shoulder. Patients with PNH may also develop gall bladder sludge, which can lead to similar symptoms to gallstones. Doctors may recommend removal of the gall bladder to alleviate symptoms of gallstones and gall bladder sludge.

Abdominal pain and difficulty swallowing

PNH patients can suffer episodic or ongoing pain in the stomach and abdominal region, as well as difficulty and pain on swallowing. The pain can be mild or very severe and may require treatment. Pain can also occur in the lower back and cause headaches.

Renal dysfunction and chronic kidney disease

The kidneys are important organs that have several essential roles in the human body, one of which is the removal of waste products from the blood. One of the recognised complications of PNH is decreased kidney function, and a significant proportion of people with PNH have chronic kidney disease. Chronic haemolysis is thought to be a root cause of kidney scarring, which in turn can impair kidney function and can result in kidney failure, one of the leading causes of death in PNH after thromboembolism.

Erectile dysfunction

Men with PNH may experience problems getting and/or maintaining erections. This occurs because the free haemoglobin released into the blood during haemolysis binds to and reduces the levels of nitric oxide in the bloodstream. This, in turn, causes the blood vessels in the penis to contract, leading to restricted blood flow to the penis which prevents an erection occurring or being maintained. Men who are experiencing erectile dysfunction should speak to their doctor as there are treatments available.

How does PNH affect quality of life?

Risk of thrombosis

Chronic haemolysis, leading to an elevated risk of thrombosis, is the central mechanism underlying the morbidities and mortality associated with PNH. With current treatments, people with PNH have shown significant reductions in TEs and can expect a close-to-normal life expectancy.

Impact of symptoms

Due to the constant haemolysis that can happen with PNH, people with the disease can experience a number of symptoms that can impair their quality of life, for example fatigue (tiredness/exhaustion), abdominal (stomach area) pain, headache, shortness of breath, dysphagia (difficulty swallowing) and erectile dysfunction.

Psychological effects

Maintaining mental wellbeing is crucial for a good quality of life. The diagnosis of PNH is a life-changing experience and some patients may benefit from professional psychological support when learning to adapt to their disease. Furthermore, it may be useful for people with PNH to have support from and share experiences with other PNH patients. Leading as normal a life as possible, including adapting physical activities, can often help patients' psychological health.

Improving quality of life

The symptoms experienced by people with PNH can be debilitating and can significantly affect their lives. However, recent advances in medicine have resulted in management and treatment options for people with PNH that can have a significant impact both on survival and quality of life.

More information on how to manage the symptoms and treatment effects of PNH and to make day-to-day life easier is provided in Section 8: Living with PNH.

How is PNH diagnosed and monitored?

Diagnosis of PNH has been known to take a long time, sometimes even months or years. This can be for a number of reasons:

- Its signs and symptoms vary greatly between different patients
- Its signs and symptoms occur in many diseases
- It is very rare and may not be the first disease that a doctor thinks of

Who should be tested for PNH?

PNH should be tested for in people who have any of the following:

- Unexplained thrombosis
- Thrombosis in unusual sites accompanied by haemolysis – such as Budd-Chiari Syndrome
- Bone marrow failure – such as AA or MDS
- Coombs negative haemolytic anaemia
- Haemolysis associated with anaemia, fatigue, smooth muscle dystonia (dysphagia, abdominal pain, dyspnoea, erectile dysfunction), unexplained visceral pain or haemoglobinuria

Due to the life-threatening and progressive nature of PNH, monitoring in these groups is really important: clone size in some people can rapidly increase over a period of several months, even in those with a small number of affected cells. Clone size does not always affect the behaviour of the disease however, and each patient should be monitored accordingly.

The highest quality test for diagnosing and monitoring PNH is high-sensitivity flow cytometry.

Flow cytometry for diagnosing PNH

Flow cytometry measures the PNH clone size using a small blood sample taken from the person's arm. It examines individual blood cells to see if they have GPI-anchored proteins on their surface, which can protect them from the immune system. If these proteins are present the blood cell is normal (type I cell), whereas if they are only partially present or completely absent the cell is a PNH type II or PNH type III cell, respectively.

Other tests

Other tests can also provide information about how PNH is affecting a person:

Full blood count

The numbers of all of the blood cell types.

White blood cell numbers

Show how well the bone marrow is functioning by indicating if it is producing normal numbers of white blood cells.

Platelet numbers

Like white blood cell numbers, the platelet numbers indicate how well the bone marrow is functioning.

Lactate dehydrogenase (LDH) level

LDH is an enzyme that is abundant in red blood cells. In PNH, LDH is released into the bloodstream when red blood cells are destroyed, and so measuring it indicates how much red blood cell destruction is occurring.

Haemoglobin levels and reticulocyte/ red blood cell numbers

The level of haemoglobin is sometimes used to indicate the amount of red blood cell destruction; however the level of LDH is a more accurate and more commonly used measure. Reticulocyte numbers are used to reveal whether the bone marrow is producing more red blood cells than normal.

Tests of kidney function

As PNH can cause kidney problems, people with PNH should have their kidney function measured by blood tests.

Bilirubin level

Bilirubin is a waste product of the breakdown of red blood cells. Levels of bilirubin can be elevated in PNH due to the increased destruction of red blood cells.

Serum ferritin test

Ferritin is a protein that stores iron within cells. In PNH, the levels of ferritin can be lower than normal due to a chronic loss of iron in the urine occurring as a result of haemolysis. The levels of ferritin can also be higher than normal in patients with PNH if therapy is used to significantly reduce haemolysis and hence the loss of iron.

Bone marrow, biopsy and aspiration

Taking a sample of the bone marrow tissue or fluid allows for examination of the cells in the bone marrow to understand how well it is working. This technique can also be used to monitor whether PNH patients have developed AA, MDS or leukaemia.

How is PNH monitored?

Doctors will monitor PNH signs, symptoms and laboratory tests closely over time.

Symptom diaries can help a patient to track how they might have been affected by PNH at different points in time. They are useful for patients to talk through with their doctor or nurse.

A diary and symptom tracker is provided at the end of this brochure to help track symptoms; it can be shared during appointments with a doctor or nurse.

How is PNH managed?

People with PNH should discuss the possible treatment options with their medical team and agree the best approach for their individual case and circumstances.

Opposite is a list of treatments that may be used to treat PNH.

Most treatments currently available are supportive therapies. This means they help resolve symptoms or treat specific complications, but they do not cure PNH.

It is important to remember that some people with PNH will not require any treatment, but just have their PNH monitored over time in case the situation changes. In individual cases, disappearance of PNH on its own, which is called spontaneous remission, has been reported.

Blood transfusions

Blood taken from voluntary donors can be given to PNH patients to increase their levels of red blood cells and improve the symptoms of anaemia they experience. Blood transfusions are not a cure for PNH, and may need to be repeated at regular intervals.

Vitamin and mineral supplements

Vitamin and mineral supplements, such as iron, vitamin B12 and folic acid, may be given as the body needs them to produce new red blood cells.

Anticoagulants

Anticoagulants, for example low molecular weight heparin and warfarin, are drugs that thin the blood to try to stop it from forming blood clots. Warfarin is an example of a medicine commonly used for this in people with PNH. The use of anticoagulants can be risky, so is only used in patients with PNH who have certain risk factors.

Erythropoietin

Some people with PNH will receive erythropoietin, which is a growth factor that encourages the bone marrow to make red blood cells. It can reduce the need for blood transfusions and can give people more energy; however, in some cases it can make symptoms worse, so is not routinely used.

Complement inhibition

Complement inhibitors, such as eculizumab (also known as Soliris), are drugs that bind and inhibit targeted components of the complement system. They work specifically for people with PNH because they are able to inhibit the complement system from destroying red blood cells.

Eculizumab is an intravenous drug which is given at fortnightly intervals into the vein. If it is indicated it should be prescribed by a physician experienced in the treatment and management of PNH. It belongs to a group of medications called monoclonal antibodies, however, unlike other drugs in this family it is 'inert' and reactions to the drug are rare. It is a long-term medication and in some countries is given in people's homes by qualified nurses.

Allogeneic bone marrow transplantation (BMT)

An allogeneic BMT is a process of replacing a person's own bone marrow cells (which produce PNH blood cells) with healthy bone marrow cells from a donor. The allogeneic BMT process usually requires the patient to undergo a period of conditioning to destroy the diseased bone marrow cells, which uses combinations of chemotherapy and/or radiotherapy and can take several days depending on the method used. Nowadays, following the development of complement inhibitors, it is rare to treat PNH with BMT and often BMT is a secondary option to complement inhibition.

Living with PNH

How do PNH signs and symptoms affect people with PNH?

The signs and symptoms of PNH are very diverse. Some people will have very few symptoms and feel well enough to carry on a normal life despite having PNH, whilst others can be very unwell needing to make changes to their daily routine. Furthermore, some patients can experience life-threatening complications. It is very difficult to predict how PNH will affect different people and how the disease might change over time.

But there is help. Advances in research and understanding mean PNH does not have as much of an impact on quality of life and life expectancy as it used to.

Work and family life

Work and family life can be challenging even when feeling well. Trying to cope with the symptoms and emotions that result from PNH can make it even more difficult. It is important for people with PNH to rationalise their priorities and think about what can be managed each day; planning time and saving energy for the things that are most important.

Work is important to most people. Patients should discuss with their employers the challenges that the disease presents. Patients on treatment may need to negotiate leave to allow them to have their infusions. The healthcare team will be able to act as an advocate in these situations.

Partners, family and friends can be a great source of help and support. Having open discussions about concerns and worries enables people to share their feelings and often helps to manage everyday issues before they get out of hand.

Emotions

It is natural to have a variety of feelings after being diagnosed with PNH. Some people may feel upset, anxious or angry, whilst others may feel relieved at finally getting a diagnosis. There is no right way to feel, and this diversity of emotions can affect not only the person diagnosed with PNH, but also the people they care for. The option of professional psychological support should be taken into consideration early. Support may be necessary not only for the people diagnosed with PNH, but also for their friends and family. A PNH diagnosis means close monitoring of the condition and of treatment, which may have an impact upon daily activities, leading some people to feel a loss of control over their lives. Being informed about the condition and involved in decision making can help to promote a sense of control in a new situation.

Emotions can affect physical health as well as mental wellbeing. It is common for people with PNH to feel stressed or anxious about their condition and the treatments they are receiving, which can cause physical symptoms. It can sometimes be difficult to identify the cause of these physical symptoms.

Sexuality and sexual functioning

PNH can cause problems getting or keeping an erection in males. In addition to this, the fatigue, anxiety and changing emotions due to PNH can also impact upon interest in sex. Do discuss this with the healthcare team as there are ways they can help.

This is a sensitive subject which can be difficult to talk about. Having an open discussion with a partner can remove the tension by explaining that a lack of interest in sex doesn't mean that there is any change in the level of affection for that person, and intimacy can also be expressed by touching, holding hands, kissing and hugging. The hospital team should be able to provide access to trained counsellors who are able to discuss feelings.

Managing symptoms and side effects of treatment

People with PNH will normally be looked after by a haematologist (a doctor specialising in blood disorders) and their team, which will often include specialist nurses, along with their general practitioner. When people experience complications due to their PNH it is important to discuss them as soon as possible as they may require the specialist care of other teams of doctors who will work with the haematologists.

Medical teams will want to know what symptoms a person has experienced and how the symptoms are affecting their life. It may be helpful for people with PNH to keep a diary of their experiences to help them remember and explain them clearly.

Some physical symptoms can be improved by changes to lifestyle, such as following a healthy diet and taking exercise where possible.

Sleep

Anxiety, worry and fear about the future can also impact on sleep. Avoiding sleeping during the day, keeping to regular sleeping patterns and doing some light exercise can aid in getting a better night's sleep. Furthermore, it can help to avoid caffeine-containing drinks and alcohol, or to take a warm bath before bed. If getting to sleep is an issue, it can help to get out of bed and go into another room, or to relax by reading or listening to music. The use of meditation and relaxation techniques can also help in promoting good sleep.

Lifestyle considerations and suggestions

Living with PNH can be difficult given the serious and rare nature of the disease. Here are some suggestions to help make day-to-day life easier:

Keep a diary of symptoms

It is important that all symptoms are openly discussed at every meeting with the healthcare team; coping mechanisms and lifestyle adaptations to symptoms, such as fatigue, may mask the disease severity or deterioration.

Tell the doctor what medications are being taken

It is important that the healthcare team are informed about all prescription, over-the-counter and herbal medications, as well as nutritional vitamins/supplements that are being taken.

Get some physical activity

It is important to get some physical activity both for physical and mental wellbeing. Physical activity can range from light passive exercises, light housework and gentle walks to more intensive activities, such as cycling or running. Healthcare teams will be able to offer advice on exercise programmes to suit each individual situation.

Notify the doctor and nurse before having any invasive procedure (e.g. dental work, colonoscopy)

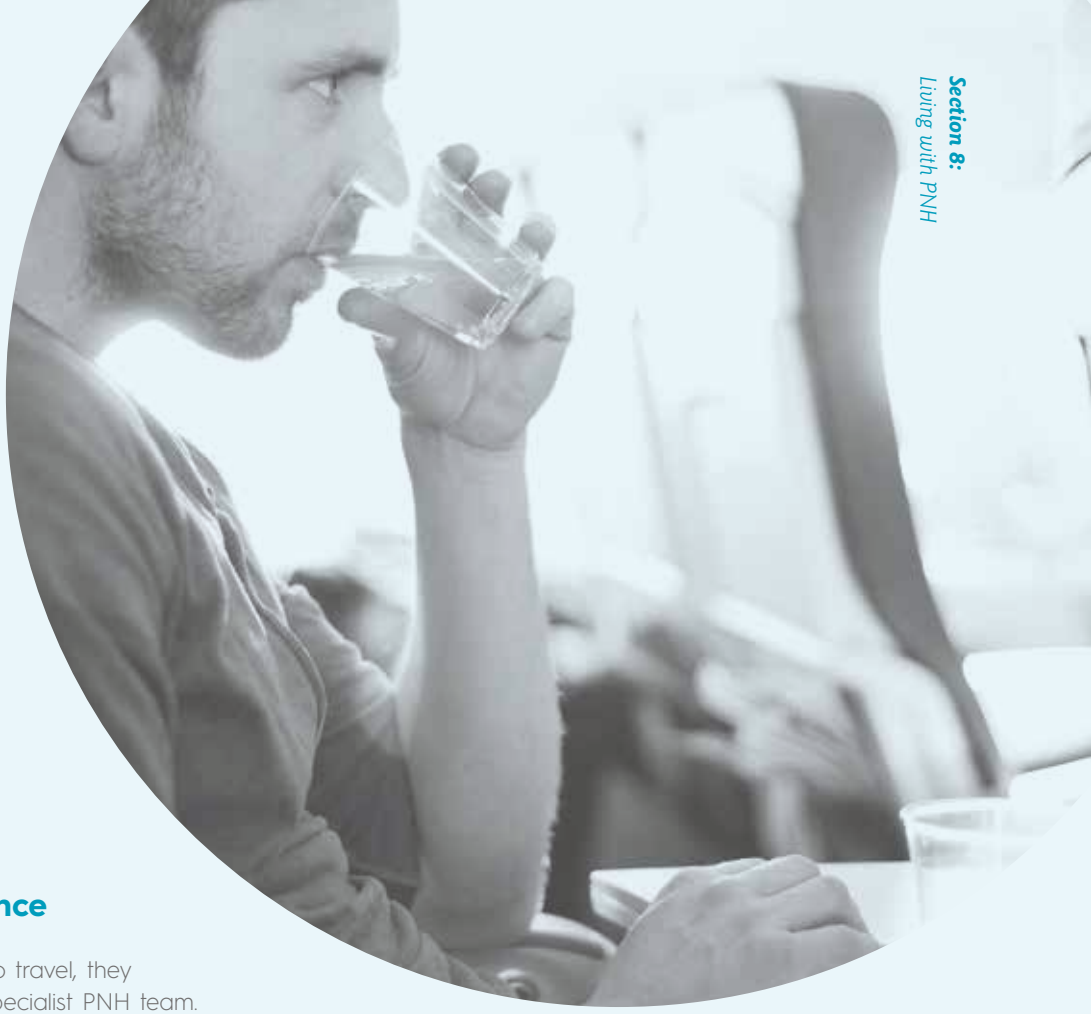
If a person with PNH is due to have surgery, their doctor may want to check their levels of blood cells and see if they need any additional support to prevent thrombosis. They may want to prescribe an antibiotic beforehand to prevent infection.

Ask for help

People with PNH can be under a lot of stress, both physically and mentally. This means that it is very common to feel overwhelmed by daily activities. Therefore, asking for support from family and friends is important to relieve some of the additional pressures caused by PNH.

Eat a healthy diet and drink plenty of water

Eating well is important for everyone, but it's especially important for people with chronic illnesses. People with PNH need to make sure they are getting the nutrients they need while avoiding unnecessary sugars and chemicals to help their bodies function well.



Travelling and insurance

If a person with PNH wishes to travel, they should discuss this with their specialist PNH team. Travel insurance provides financial protection if something goes wrong when people are away. When booking insurance, insurers will often ask for details of travellers' ages, destination of travel and any pre-existing medical conditions, including PNH. It is therefore helpful to have these details, plus any details of treatment, ready to provide to the insurance company. If possible make sure that the insurance company has a specific code for PNH.

Pregnancy

For women with PNH, pregnancy can be risky for both the mother and the child. Women who have PNH and are hoping to become pregnant should speak to their specialist PNH team to discuss the best options to reduce the risk of complications during pregnancy. Close communication between the obstetric team and the haematology team is key to a safe mother and baby.

Contraception

For people with PNH, the safest methods of contraception are either the progesterone-implanted coil or condoms. The combined oral contraceptive pill should be avoided because it can result in an increased risk of developing a blood clot. Patients should discuss contraception with their healthcare team, who will be able to provide more information and advice.

Surgery

Surgery can pose a number of risks for people with PNH. It can increase activity of the complement system, which causes haemolysis. In this context, surgery can increase the risk of blood clots and can cause serious bleeding in people with a low platelet count (which can occur in PNH).

People with PNH who require surgery should speak to their specialist PNH doctor to ensure that any special measures can be put in place.

Complementary therapies

Complementary therapies are those used alongside traditional medical treatments, such as counselling, aromatherapy, massage therapy, meditation and visualisation techniques. They are often used to promote physical and emotional wellbeing, and may help to improve quality of life, reduce stress and anxiety, improve sleep patterns and relieve some symptoms. Healthcare teams will be able to offer advice on therapies that may be safe and appropriate for an individual situation.

Talking about PNH

Questions to ask the doctor/ nurse about PNH

A good relationship between people with PNH and doctors/nurses is important for the successful management of the disease. People with PNH might find it useful to write down questions they want to ask their doctor or nurse before their appointments. A useful starting point might be to ask:

- *What is PNH?*
- *What is the underlying cause of PNH?*
- *How is PNH diagnosed?*
- *How is PNH monitored/what do you look for?*
- *How will PNH be managed?*

In addition, it is crucial that doctors and nurses are fully informed of all symptoms, even if they don't appear to be important or related to PNH – details of when the symptoms started, how often they happen and how bad they get should be provided.

The diary and symptom tracker at the end of this brochure has space to write down questions and record symptoms over time.

Communicating with family, friends and carers

It is important for the family and friends of a person with PNH to fully understand how the disease might affect them, to help them to understand how the person might be feeling and how they can help.

Being diagnosed with PNH can bring a variety of emotions and it can be a stressful time. Sometimes it is difficult to speak with family members about PNH; friends and family often want to help, but do not know how to start conversations for fear of upsetting their loved one.

Starting the conversation may help others to feel more comfortable when talking about their concerns. Discussing the disease and the impact of living with PNH on daily life may be a way to share feelings and questions, and to give and receive support.

It can help to specify the topic of concern beforehand, for example 'I'm worried about my haemoglobin level', in order to help focus the conversation on the main issues.

Sometimes it may be helpful to talk to a specialist; this could include a member of the hospital team, a specialist nurse, a psychologist or one of the support organisations listed at the end of this booklet.

Communicating with children

When a parent has PNH, it can be difficult to know what to say and what not to say about the disease to their children.

Any discussions about the disease or the treatment should reflect the age of the child. It is often best to be open because children can sense changes in the family dynamic and can benefit from understanding why a parent may be feeling more tired or is unable to be as active in their care as usual.

Hear from another patient with PNH

Lars is a patient with PNH from Germany. He has kindly offered to share his story as a means of support and information for other patients and their families, friends and carers.

Name: *Lars*

Age: *29*

Location: *Stuttgart, Germany*

Hobbies: *I am an active person and try to make the most of the joys in life. I love various sports and outdoor activities, and I'm addicted to travel.*

What happened when you first started to develop symptoms of PNH?

In 2008 I suffered an autoimmune-induced inflammation of my liver (sarcoidosis), which was successfully cured with steroids. After I had recovered my blood counts started to decrease so my doctors examined my blood and took a biopsy of my bone marrow. They diagnosed me with suspected low-grade myelodysplastic syndrome with no indication for treatment.

Following this I suffered with poorly-managed hypothyroidism (an under-active thyroid) and liver inflammation, which greatly affected my quality of life. Because I was so tired of seeing doctors and hospitals I decided to carry on with my life and push my health issues to the back of my mind. However, in the years that followed I gradually lost my vitality, energy, strength and concentration.

I struggled to carry on with my career and part-time studies and nobody understood what was going on. My relatives and friends grew concerned; they told me I was being way too active and that I should slow down every once in a while.

I looked pale, my eyes were yellowed and I felt tired all of the time.

Tell us about the events leading up to your PNH diagnosis

During a stressful period in my life I suffered a huge haemolytic crisis. It occurred around New Year's Eve 2013 while I was preparing for an important exam. I was suddenly hit with excruciating abdominal pain and sickness, which left me confined to my bed for days. My mother took me to the hospital, where the doctors conducted a whole host of medical investigations. In order to relieve the pain in my stomach I was prescribed morphine, however this provided no relief.

As a last resort a physician in the provincial hospital suggested a PNH test, which came back positive. I was given a steroid-based treatment and was able to leave the hospital after a few days with less pain but in an even worse condition. This provincial hospital had no experience with PNH so they sent me to see another doctor in a university hospital a few weeks later.

At the university hospital I was told that information about PNH is limited and that the future is "not going to be easy for me". At this point I felt completely helpless and alone.

I was prescribed blood thinners and my steroid dose was reduced so my abdominal pain came back immediately. It seemed as though an appropriate treatment did not exist and I didn't receive any useful information about my disease from the physicians I saw at the time.

By this point the haemolysis had ruined my entire physical constitution. I was demoralised and lost the will to survive. I started to conduct my own research, which involved staying up all night reading anything I could find; I even read dissertations and medical reports from the internet. I eventually found out that the University Hospital of Ulm is well known for specialising in the treatment of patients with PNH and that there is a drug named eculizumab (Soliris) that could help me.

What treatment did you receive for your PNH and how did it affect you?

After receiving infusions with eculizumab (Soliris) my fatigue disappeared and I was able to stop using the blood thinners and steroids. Luckily I did not experience any side effects of therapy and I am thankful for this unbelievable improvement in my quality of life. My sickness did not improve initially because the haemolysis gave me gallstones. Once my gall bladder was removed I was able to live with PNH without any symptoms.

What aspects of medical care have you found most useful, and what have you found most frustrating?

For me, the most useful aspect of medical care is that we have a commendable healthcare system in Germany that offered me help and treatment once I had found the right specialist.

I felt very frustrated when I was given a diagnosis that felt like a death sentence without any accompanying help or support. There wasn't any appropriate information available and my doctors weren't able to offer me the necessary psychological help to deal with the diagnosis, especially at such a young age.

I would have felt more comfortable if some of the doctors I met had sent me to a specialised treatment centre instead of letting me suffer with 'watch and wait' therapy.

How has your PNH affected you and those around you?

Facing a rare, potentially life-threatening disease changed my life entirely. The disease process lasted years before I was diagnosed. When I was eventually diagnosed it was bittersweet; like a relief and a burden at the same time. The emotions became overwhelming so I decided to seek professional psychological help, which was very important as I couldn't handle the new situation and obtain a positive attitude for the future on my own. I realised that my family and friends had become very worried about seeing me in such poor health.

Because PNH is not a well-known disease, and from the outside patients can often look relatively healthy, it is difficult for people without PNH to understand how the disease affects sufferers both physically and mentally. Some people who are not lucky enough to get an early diagnosis may develop depression because it is assumed that they are mentally ill due to the lack of physical reasons for their symptoms.

It has been a struggle to maintain a normal life and to be taken seriously by society and healthcare professionals.

How do you feel about the future?

At present I feel blessed that I found a reliable, dedicated doctor and a treatment that enables me to live a nearly normal life. I found new confidence and I'm looking forward to my future. Having a chronic illness such as PNH is not a gift, however if you open your mind and learn to accept the new situation the process can show you the value of life and the preciousness of even the small things.

If you met a newly diagnosed PNH patient today, what advice would you give to them?

If you have been newly diagnosed with PNH then please know that you don't have to feel alone. All other patients with PNH know what you are going through and how you might be feeling about your new diagnosis. Trust that your doctors will help you the best they can and know that the research and development for our disorder is based on a high level of science. I wish you all the best and hope that my story gives you confidence for the future!

Patient symptom diary

This diary is designed to help people with PNH to keep a record of any symptoms or problems they are experiencing. There is also space to record hospital appointments and any questions to ask the doctor or nurse. The information within the diary can be discussed with the nurse/doctor at the next visit. They may also ask their nurse/doctor to record important information about their illness for them.

Appointments

Keep track of upcoming hospital appointments in the table below:

Date	Time	Clinic/hospital	Notes

Date	Time	Clinic/hospital	Notes

Symptom diary

This symptom diary can be used to track any symptoms that may be experienced in between visits to the hospital. Take a few minutes to update the diary every week.

Please add notes into the comments section of the diary to give additional details around any symptoms that are experienced.

Notes:

Month _____

Tiredness (lack of energy)

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Abdominal pain (stomach pain)

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Haemoglobinuria (dark coloured urine)

Rate the colour of the urine you have experienced from 1-5

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Shortness of breath (difficulty breathing)

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Chest pain

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Trouble swallowing

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Erectile dysfunction (men only)

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Leg pain or swelling

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Weakness (lack of strength)

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Headache

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Problems with concentration and memory

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Difficulty performing everyday tasks

How would you rate your symptoms?
(1 is mild and 10 severe)

Day	Week 1	Week 2	Week 3	Week 4	Week 5
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

Please provide an example:

Was this due to –

Shortness of breath ☐

Tiredness ☐

Pain ☐

Other ☐

If other, please give details:

_____

_____

_____

_____

List any other symptoms or anything else that is different from usual for you. Have your symptoms stopped you from doing anything else that is normal for you? If yes please explain.

_____

_____

_____

Note down any information you would like to discuss at your next hospital appointment, or any questions you have.

_____

_____

_____

Where can I get more information?

The following websites contain information and advice surrounding PNH and other rare diseases.

PNH Alliance:
www.pnh-alliance.org.uk

Asociación HPN:
www.hpne.org

ORPHANET:
www.orpha.net

EURORDIS:
www.eurordis.org

HEMATOSLIFE:
www.hematoslife.org

AIEPN:
www.aiepn.it

STEM ONLUS:
www.astem.it

ISS:
www.iss.it/cnmr/index.php?lang=1

PNH National Service (UK):
www.pnhleeds.co.uk

PNH UK:
www.pnhuk.org

PNH I Aplastische Anämie e.V.:
http://www.aplastische-anaemie.de/

Stiftung Lichterzellen:
http://www.lichterzellen.org/

Facebook: PNH Foundation Group:
https://www.facebook.com/PNHFoundation?fref=ts

DGHO (English):
https://www.onkopedia-guidelines.info/en/onkopedia/guidelines/paroxysmal-nocturnal-hemoglobinuria-pnh/@@view/html/index.html

DGHO (German):
https://www.onkopedia.com/de/onkopedia/guidelines/paroxysmale-naechtliche-haemoglobinurie-pnh/@@view/html/index.html

European Society for Blood and Marrow Transplantation (EBMT):
www.ebmt.org

Glossary

A

Anaemia: A decrease in the amount of red blood cells or haemoglobin in the blood.

Anticoagulation therapy (anticoagulants): A class of drugs that work to prevent the coagulation (clotting) of blood.

Aplastic anaemia (AA): A disorder in which the bone marrow decreases or stops blood cell production.

Artery/arteries A type of blood vessel that carries blood from the heart to various parts of the body.

B

Blood clot/thrombosis: Blood clots form when parts of the blood in the body clump together, potentially blocking veins and arteries. Blood clots can be fatal as they may cause a heart attack, stroke and organ damage, among other problems.

Bone marrow: The substance found inside the cavities of bones.

Bone marrow failure: When bone marrow is unable to produce sufficient amounts of blood cells to supply the needs of the body.

Bone marrow transplantation (BMT): Is the transplant of stem cells (usually from bone marrow or blood). The person's own stem cells may be used (autologous transplant, not used in PNH) or the cells may come from a donor (allogeneic transplant), as is the case in PNH.

C

Clone size (referring to PNH): The percentage of blood cells in the body that are affected by PNH. Often referred to as small/large clone.

Complement system: A part of the body's immune system; a group of ~25 proteins that work together to help the antibodies and phagocytes destroy bacteria viruses and abnormal cells.

D

Dysphagia: Difficulty or discomfort in swallowing, as a symptom of disease.

Dyspnoea: Difficulty in breathing.

E

Eculizumab (Soliris): A type of drug called a complement inhibitor. It works by stopping the complement system from attacking the blood cells.

Erectile dysfunction: A condition found in men that affects their ability to achieve and maintain an erection.

Erythrocyte: A red blood cell that contains haemoglobin and transports oxygen to the tissues.

F

Flow cytometry: A technique for counting and examining microscopic particles, such as cells and chromosomes.

G

GPI-anchor protein: Protein anchors that attach protective proteins to surface of cells thereby protecting cells from attack by the complement system.

H

Haemoglobin: The substance in red blood cells that carries oxygen in the blood.

Haemoglobinuria: A condition in which the substance in red blood cells that carries oxygen in the blood, haemoglobin, is found in abnormally high concentrations in the urine.

Haemolysis: The destruction of red blood cells by the complement system, a part of the body's natural defence system. Haemolysis is the main cause of the signs, symptoms and serious health problems in PNH, including some that are life-threatening.

Haemolytic: Relating to haemolysis.

Haemolytic anaemia: A decrease in number of red blood cells due to haemolysis, the abnormal destruction of red blood cells.

L

Lactate dehydrogenase (LDH): An enzyme found in red blood cells that is released during haemolysis. Testing for LDH can help show how much haemolysis is happening in the patient.

Leukocyte: A type of white blood cell that helps to protect the body against infection.

M

Myelodysplastic syndrome (MDS): MDS is a blood-related condition that occurs as a result of ineffective production of blood cells. People with MDS can develop severe anaemia and require blood transfusions. In some cases, the disease can worsen and the person can develop low blood counts caused by progressive bone marrow failure.

Mutation: A change in genetic material.

P

Paroxysmal nocturnal haemoglobinuria (PNH): A disease where red blood cells are created with varying amounts of or no protective protein. This causes them to burst (a process called haemolysis) and can result in serious health problems and life-threatening complications.

PIG-A gene: The PIG-A gene is the gene responsible for making proteins called glycophosphatidylinositol anchors. These anchors attach protective proteins to the cell surface, protecting the cells from attack by the complement system.

Platelets/thrombocytes: Are a component of blood whose function is to stop bleeding by clumping and clogging blood vessel injuries.

PNH clone cells: Cells that have been affected by PNH. PNH clones are lacking a protein that anchors other proteins to the outside of cells.

Protein: Complex molecules composed of amino acid chains that are fundamental components of all living cells.

Pulmonary hypertension (PHT): A type of high blood pressure that affects the arteries in the lungs and the right side of the heart.

R

Reticulocyte: Reticulocytes are immature red blood cells that are produced in the bone marrow. They eventually enter the bloodstream and become mature red blood cells.

T

Thrombocytes/platelets: Are a component of blood whose function is to stop bleeding by clumping and clogging blood vessel injuries.

Thromboembolism: The obstruction of a vein or artery by a blood clot from another site.

Thrombosis/blood clot: Blood clots form when parts of the blood in the body clump together, potentially blocking veins and arteries. Blood clots can be fatal as they may cause a heart attack, stroke and organ damage, among other problems.

Thrombotic event (TE): An event relating to the formation of blood clots in places that may cause obstruction to the blood flow.

V

Vein/veins: In the circulatory system, veins are blood vessels that carry blood toward the heart.

Produced by the Nurses Group of the European Society for Blood and Marrow Transplantation (EBMT NG), this brochure was made possible by financial support received from Alexion Pharmaceuticals.

EBMT
European Society for Blood and Marrow Transplantation

Date of update: October 2015