PNH RTB Project Summaries

1) Immunological repertoire analysis by next generation sequencing

This PhD research project aims to better understand how the immune system may contribute to the development of PNH. Researchers will study a type of immune cell called a T cell, which may play an important role in the disease.

Using advanced genetic sequencing techniques, the team will compare immune cells from people with PNH to those without. They will also compare samples from the blood and bone marrow to learn more about how the immune system interacts with the bone marrow environment.

The findings may help researchers understand why PNH cells are able to grow and expand, potentially leading to improved treatments and better disease management in the future.

2) Bone marrow failure study (ongoing)

This study aims to understand why bone marrow failure occurs in people with PNH. Researchers will examine both the abnormal blood-forming stem cells that carry the PNH mutation and the environment in which these cells develop.

Current treatments are effective at reducing many of the symptoms and complications of PNH, but they do not address the underlying cause of the disease. By learning more about how PNH develops and progresses, this research may help identify new ways to treat the condition at its source.

3) Haemolysis study (ongoing)

A major feature of PNH is the destruction of red blood cells, known as haemolysis. This study aims to better understand the different ways haemolysis occurs in PNH and why some patients respond differently to treatment.

Researchers will investigate factors within the patient's own cells, as well as the effects of complement-inhibiting medicines currently used to treat PNH. The study will also develop new laboratory tests to measure haemolysis and monitor treatment effectiveness.

The knowledge gained may help doctors personalise treatment and improve outcomes for patients who continue to experience symptoms despite current therapies.

4) COVID-19 vaccination study

This study investigates how people with PNH and aplastic anaemia respond to COVID-19 vaccination.

Researchers will measure both antibody and immune cell responses before and after vaccination and compare these results with responses seen in healthy volunteers. The study will also examine how long vaccine protection lasts.

Because people with PNH and aplastic anaemia may have differences in immune function or may be receiving treatments that affect the immune system, understanding vaccine responses is particularly important. The findings could help guide future vaccination strategies and ensure patients receive the best possible protection against COVID-19.

5) Clonal trajectories

This study focuses on understanding how blood-forming stem cells change and develop over time in patients with aplastic anaemia and PNH.

While many patients respond well to treatment, a small number later develop other blood disorders. Researchers will use advanced genetic techniques to investigate how different groups of blood stem cells grow, change and compete over time.

The aim is to identify patterns that may help predict which patients are at higher risk of disease progression, allowing doctors to monitor patients more closely and make more informed treatment decisions.

6) Bone marrow clonality

This research seeks to understand how PNH and related bone marrow disorders develop and change throughout a patient's life.

Using advanced genetic testing and laboratory models, researchers will study changes in blood stem cells, immune system activity and signals within the bone marrow. They will investigate why some patients respond well to treatment while others experience different disease courses or complications.

The long-term goal is to develop personalised approaches to patient care, helping clinicians better predict outcomes and choose the most appropriate treatments for individual patients.

7) PNH Breakthrough haemolysis study (ongoing)

Modern treatments have greatly improved the lives of people with PNH, but some patients still experience episodes of "breakthrough haemolysis", where red blood cells are damaged despite treatment.

This study aims to understand why these episodes occur by examining blood samples from patients receiving different types of treatment, as well as from patients who are not currently receiving complement inhibitor therapy.

By identifying the causes of breakthrough haemolysis, researchers hope to improve treatment strategies and reduce the impact of these episodes on patients.

8) PNH novel AH50 assessment

This project aims to develop and evaluate a new laboratory test that measures activity within the complement system, the part of the immune system responsible for red blood cell destruction in PNH.

Researchers hope this test will provide a more accurate way of monitoring how well treatments are working and help identify patients who may be at risk of breakthrough haemolysis.

The findings may lead to improved monitoring of treatment effectiveness and support more personalised care for people living with PNH.

PNH RTB Publication Abstracts

Holt et al. (2025) Factor bb as a biomarker during breakthrough hemolysis in paroxysmal nocturnal hemoglobinuria

PNH is a rare blood disorder in which red blood cells are vulnerable to attack by the body's complement system, leading to their destruction (haemolysis). Although complement inhibitor therapies have transformed the treatment of PNH, around 10% of patients still experience episodes of breakthrough haemolysis, where red blood cell destruction returns despite treatment, often following infections or other triggers that increase complement activity. Factor Bb (FBb) is a key component of the alternative complement pathway and may increase when this pathway becomes activated. This study aimed to investigate whether FBb levels reflect complement activity in patients with PNH and whether they rise during episodes of breakthrough haemolysis. The study found that FBb levels increased during episodes of breakthrough haemolysis and were associated with increased red blood cell destruction, suggesting that FBb could become a useful marker for monitoring complement activity and guiding treatment decisions in PNH.

Holt et al. (2025) The effect of breakthrough hemolysis on complement factor h and factor I levels in paroxysmal nocturnal hemoglobinuria

Although modern complement inhibitor treatments have greatly improved outcomes for PNH patients, some still experience episodes of increased red blood cell destruction, known as breakthrough haemolysis. Complement Factor H (CFH) and Complement Factor I (CFI) are natural proteins that help control complement activity and protect healthy cells from damage. Because some patients appear to experience breakthrough haemolysis more frequently than others, this study aimed to investigate whether levels of CFH and CFI differ between patients with PNH and whether these levels change during episodes of breakthrough haemolysis, which could provide new insights into disease activity and treatment response. The study found that CFH levels increased during episodes of breakthrough haemolysis, while CFI levels remained largely unchanged. Patients with a history of breakthrough haemolysis had lower baseline CFI levels, suggesting these proteins may help improve understanding of disease activity and identify patients at greater risk of breakthrough haemolysis.

Chapman et al. (2025) Clonal architecture and dynamics of somatic evolution in aplastic anemia and paroxysmal nocturnal hemoglobinuria

Aplastic anaemia (AA) is a rare and serious bone marrow failure disorder in which the immune system attacks the blood-forming stem cells needed to produce healthy blood cells. While some patients respond well to immunosuppressive treatment, others do not, and a proportion go on to develop related blood cancers or PNH. This study used advanced genetic techniques to examine how AA and PNH develop over time by tracking changes in individual blood stem cells. The researchers found that patients follow different disease pathways, with some developing genetic changes that help cells evade the immune system and others acquiring mutations more commonly associated with blood cancers. Importantly, many of these disease-related genetic changes appeared years, and sometimes even decades, before symptoms developed. The findings improve our understanding of how AA and PNH evolve and suggest that future patient care could be improved by incorporating genetic and clonal information into diagnosis, prognosis, and treatment decisions, allowing therapies to be better tailored to individual patients.

Holt et al. (2024) A review of the pathophysiology of paroxysmal nocturnal hemoglobinuria

PNH is a rare blood disorder caused by genetic changes that leave blood cells without important protective proteins, making them vulnerable to attack by part of the immune system known as the complement system. This can lead to red blood cell destruction, anaemia, blood clots, fatigue, and other serious complications. The

introduction of complement inhibitor therapies has transformed outcomes for patients, but challenges remain, including breakthrough haemolysis, ongoing anaemia, and an increased risk of infection. This review brings together current knowledge on how PNH develops, how it affects patients, and how modern treatments work. It also explores the important role of complement regulatory proteins, which may help explain why some patients respond differently to treatment than others. By highlighting recent advances and gaps in knowledge, the review identifies key areas where further research could improve the understanding and management of PNH.

Pike et al. (2023) Paroxysmal Nocturnal Haemoglobinuria (PNH) Arising from Non-Canonical Mutations

PNH is usually caused by changes in a gene called PIGA, which lead to the loss of important protective proteins on blood cells. Without these proteins, red blood cells become vulnerable to attack by the body's complement system, resulting in complications such as haemolysis (destruction of red blood cells) and an increased risk of blood clots. While PIGA mutations account for most cases of PNH, rare mutations in other related genes have also been reported. Among patients receiving treatment at the Leeds National PNH Centre, a small group have shown clinical features that differ from what is typically expected in PNH, including signs of increased inflammation. The study identified rare changes in genes other than PIGA in several patients with unusual features of PNH, including inflammation and recurrent skin rashes, highlighting the importance of recognising alternative genetic causes that may help support more personalised care in the future.

Pike et al. (2023) Sars-Cov-2 Antibody and T-Cell Responses in Patients with Paroxysmal Nocturnal Hemoglobinuria and Aplastic Anemia after Four COVID-19 Vaccinations

There is limited information on how well people with paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia (AA) respond to COVID-19 vaccination. Previous research from the Leeds PNH service showed that antibody responses after the first COVID-19 vaccine dose were lower than those seen in healthy individuals but improved significantly after the second dose. This study extended those findings by examining immune responses in 244 patients with PNH and/or AA and 49 healthy volunteers following up to four COVID-19 vaccinations, assessing not only antibody levels but also the ability of those antibodies to neutralise the virus and the development of vaccine-induced T-cell immunity. The study found that although immune responses to the first two COVID-19 vaccinations were generally lower in patients with PNH and AA than in healthy volunteers, both

antibody and T-cell responses improved with each additional vaccine dose, highlighting the importance of repeated vaccination in this patient group.

Pike et al. (2022) COVID-19 vaccination antibody responses in patients with aplastic anaemia and paroxysmal nocturnal haemoglobinuria:

Researchers at the UK National PNH Service in Leeds investigated how well people with paroxysmal nocturnal haemoglobinuria (PNH) and aplastic anaemia responded to COVID-19 vaccination. After the first vaccine dose, patients were less likely than healthy volunteers to develop antibodies against the virus (63% versus 95%), and antibody levels were lower across all disease groups. However, after the second vaccine dose, antibody responses improved dramatically, with 99% of patients developing antibodies, a rate comparable to healthy volunteers. These findings are reassuring and suggest that, although patients with PNH and aplastic anaemia may have a weaker response to a single COVID-19 vaccination, completing the full vaccination schedule results in strong immune responses in almost all patients.