A global policy consensus paper to address remaining unmet medical needs for people living with PNH

Partnering
4 PNH
Aspire for change

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Association canadienne de l'anémie aplasique et de la myélodysplasie

PNH CANADIAN ASSOCIATION OF PNH PATIENTS

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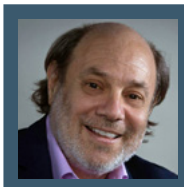


Barry Katsof
President and Founder, Canadian Association of PNH Patients, Canada

"Raising awareness is a vital key to shortening the Patient Journey from first symptoms to diagnosis. Awareness will hopefully impress upon the Regulators why speedy access to treatment is so vital to saving patient's lives".

Dr Christopher Patriquin*
Consultant Haematologist, University Health Network, Toronto General Hospital, Canada

"People around the world are diagnosed with PNH, but targeted therapies are available in only a fraction of those countries. This paper will hopefully raise awareness of PNH, how to recognise and diagnose it, the impact of it on patients living with the disease, and shine a spotlight on the need for treatments to be made available as widely and affordably as possible"

Cindy Anthony
Executive Director, Aplastic Anaemia and Myelodysplasia Association of Canada, Canada

"Not only is it important to raise awareness, but all patients must have equitable access to new treatments in a timely manner".

Emmelie Persson
Head of MACS Pegcetacoplan, Global Medical Affairs and Clinical Science, Swedish Orphan Biovitrum AB, Sweden

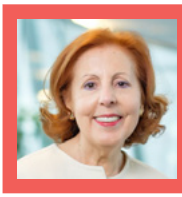
"It is really powerful when various stakeholders with different experiences but with common goals partner together to create a sustainable path for the rare disease community. This can lead to increased quality of life for patients, here represented by people living with PNH, and gains for society in general, as more innovation reaches the patients".

István Ujhelyi
Member of the European Parliament, Socialists & Democrats, Hungary

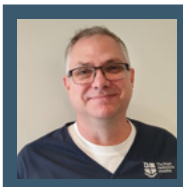
Jordi Cruz
President, Asociación de Hemoglobinuria Paroxística Nocturna, Spain

"Rare disease patients need answers to their condition and its symptoms. Political decisions should respond to the needs of patients, both in early diagnosis and in offering treatment as soon as possible, acting with equity".

Louise Arnold
PNH Specialist Nurse, Leeds teaching Hospitals NHS Trust, United Kingdom

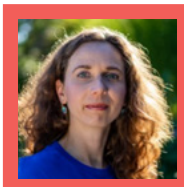


Maria da Graça Carvalho
Member of the European Parliament, European People's Party, Portugal



Michael Brown
Clinical Nurse Consultant, Royal Melbourne Hospital, Australia

"The global consensus paper is an essential first step in maintaining best standards practice in the care and management of people living with PNH irrespective of which country they live in around the world".



Mihaela Veringa
Director Access Policy Strategy and Government Affairs, Swedish Orphan Biovitrum AB, Switzerland

"This partnership and the consensus paper are a testament to the unmet medical needs of people living with PNH around the world and that we, as a collective, need to work together, to address these needs".

Dr Morag Griffin
Consultant Haematologist, Leeds teaching Hospitals NHS Trust, United Kingdom

"A global consensus policy is very important to raise awareness of PNH, an ultra rare condition, to increase awareness and diagnosis, but also to improve management for patients, increasing access to therapy worldwide, and leading to a more patient centred approach to treatment as options increase, supporting patients to live full and active lives, and reducing complications".

Olena Wagner
Chair, PNH Ukraine, Switzerland

"People living with PNH across Europe are still facing significant hurdles in access to diagnosis, care, and treatment. This consensus paper is drawing attention to current unmet needs and calling for political action to improve patients' quality of life".

Stelios Kympouropoulos
Member of the European Parliament, European People's Party, Greece

"While improving access to therapies and treatments is of critical importance for PNH patients, we must also consider the psychosocial and economic burden of living with a rare disease. As this consensus paper highlights, policies and frameworks on rare diseases must holistically address patients' needs and support necessary actions to ameliorate their quality of life"

Medical writing provided by L.E.K Consulting, Secretariat provided by Evoke Incisive Health

Disclosure of conflicts of interest

The experts involved in the Partnering4PNH initiative and in the drafting of the consensus paper participated on a voluntary basis.

Dr Christopher Patriquin works and has worked with Alexion, Apellis, Amgen, Novartis, Sobi, Roche, BioCryst, Sanofi, Takeda (board, consultancy and speaking honoraria).

The Canadian Association of PNH Patients has in the past received financial support from Sobi.

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Foreword

Paroxysmal Nocturnal Haemoglobinuria (PNH) is one of 6-7,000 rare diseases known globally and is estimated to affect between 5 and 20 people per million. The life of a person living with PNH is far from simple, with fatal symptoms such as thrombosis, renal insufficiency, bone marrow failure but also nonfatal manifestations of the disease such as severe anaemia and fatigue. Furthermore, the heterogeneity and rarity of PNH symptoms complicate the diagnosis journey and ultimately the outcomes for people living with PNH across the world.

For example, a PNH diagnosis takes on average between 2 and 5 years which creates a profound negative financial and emotional impact on the patients and their families. To improve the long diagnostic journey, eliminate unequal access to treatments and offer a chance to a better quality of life for people living with a rare disease across Europe and around the world, it is our duty as policymakers to continue to raise awareness on rare diseases such as PNH and inspire continuous action at European level and across the world. In Europe, for example, we are currently faced with an important task of the revision of the Orphan Medicinal Products and Paediatric Regulation, a task which, if done right, can generate positive impact for patients and the healthcare systems for the years to come.

Co-chairing the Partnering4PNH initiative gave us the opportunity to listen closely to the challenges of patients and healthcare professionals from different countries across the world and this experience has strengthened our commitment to push for further positive change for people living with a rare disease such as PNH.

The expert group of Partnering4PNH came together with a clear task to highlight the unmet needs of people living with PNH and propose policy recommendations to address those needs. As policymakers, we can bring forward many actions to improve patients' chances of receiving a better quality of life and care. Only through partnership, continuous and open dialogue we can strive for long term improvements.
We are honoured to be part of Partnering4PNH as it complements our work in the European Parliament and in our constituencies, to raise awareness and address the unmet needs of people living with rare diseases – whether this means contributing to building a stronger research and innovation framework for healthcare in Europe through the "Pharmaceutical Strategy" or addressing broader issues to make our healthcare systems more sustainable and resilient. We remain committed to work with our colleagues in the European Parliament along with all other stakeholders to make sure that this policy consensus paper supports the collective effort of addressing the challenges faced by the PNH community.

MEP István Ujhelyi
(Political Co-chair)

MEP Stelios Kympouropoulos
(Political Co-chair)

MEP Maria da Graça Carvalho
(Political Observer)

Section 1. Executive Summary

PNH is an acquired ultra-rare, chronic, potentially life-threatening disease of the blood, which has a significant impact on the quality of life (QoL) of people living with it. Whilst life expectancy has improved to near normal over the years since the approval of the first complement inhibitor treatment in 2007, many people living with PNH still report debilitating complications that affect their ability to complete daily activities.

As research in PNH is evolving and the therapeutical benefits are improving, healthcare policies around the world must adapt and evolve with science. This global policy consensus paper aims to highlight the gaps and challenges faced by people living with this disease when accessing care and adequate treatments and issues a set of policy recommendations to support this scientific journey. It examines policies accompanying the patient journey, from presentation of symptoms to diagnosis, to access to care, as well as the impact on mental health. This policy consensus paper reflects the discussions of the Partnering4PNH expert group, a global multistakeholder policy initiative which brings together PNH healthcare professionals (HCPs), nurses, patients, and patient organisations (POs) from the United Kingdom (UK), Spain, Ukraine, Canada, and Australia.

Overview of Our Policy Recommendations

Our recommendations are to:

1. Increase awareness on PNH. Even though research in PNH has increased in the last decade, there is still a lack of awareness that often results in a prolonged diagnosis journey or misdiagnosis. Early diagnosis can significantly improve patients' outcomes and reduce the negative financial and emotional impact on their wellbeing and the sustainability of healthcare systems.

2. Reduce inequalities and expedite access to treatment. The low prevalence of PNH and lack of awareness and understanding of PNH is coupled with significant access barriers. The willingness among decision-makers to invest in treating ultra-rare disease patients varies significantly across countries, as reflected in the heterogenous access journey for orphan medicinal products from regulatory approval to reimbursement. Partnering4PNH strongly encourages the use of value assessment frameworks for rare diseases to inform health decision-making.

3. Improve understanding of PNH through the use of specific HRQoL/PRO measurements. To support the adoption and use of innovative therapies that address the unmet needs of PNH patients, measurement and collection of QoL data is vital to understand the holistic impact of PNH. The frequency and severity of specific symptoms must be captured from a physical, psychological, functional, and social perspective with a disease-specific instrument.

4. Empower patients and their caregivers in decision-making. Health literacy and capacity-building, shared decision-making, and support for self-management are all equal components of patient empowerment that can help in building modern healthcare systems based on effectiveness, access, and resilience. Partnering4PNH strongly supports the empowerment of PNH patients as a key element to managing the disease.

5. Strengthen role of nurses in PNH patient care. Since PNH is a lifelong ultra-rare disease, PNH specialised nurses play an important role for patients throughout the pathway of care, from investigations and diagnosis, through to treatment and palliative care. Nurses are often considered a primary source of support for patients when dealing with haemolytic events, infections, or side effects from medications. As such, nurses must stay informed with the latest disease information and management strategies, for example by including PNH as part of formal nurse training curriculum. Furthermore, as they spend an extensive time with PNH patients, their knowledge can play a key role in supporting HCPs' understanding of the disease and burden of persistent symptoms.

6. Build a more resilient ecosystem for rare disease research and innovation. The past 20 years of advances in innovation for rare diseases in Europe are directly linked to the establishment, in the year 2000, of the European Orphan Medicinal Products (OMP) and Paediatric Regulation. People living with a rare disease could only access eight treatments before the adoption of the EU OMP Regulation. This number has increased to almost 190 and it also includes treatments that people living with PNH can access today in Europe and worldwide. To expedite access to these medicines, regulators, Health Technology Assessment (HTA) bodies, payers, patients, and industry need to work closer to build a more resilient ecosystem for future rare disease research and innovation, for the next 20 years.

Section 2. Introduction

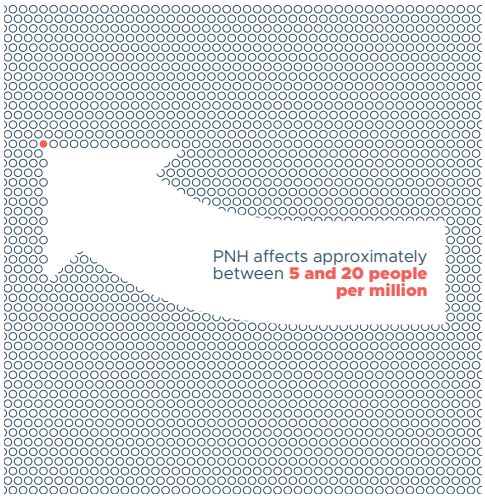
i. What is Paroxysmal Nocturnal Haemoglobinuria?

Paroxysmal Nocturnal Haemoglobinuria (PNH) is an acquired ultra-rare, chronic, potentially life-threatening haematological disease. Blood cells, including red blood cells (RBCs), white blood cells (WBCs), and platelets, from people living with PNH, lack various cell surface proteins, making them highly susceptible to complement mediated damage and haemolysis.[1] PNH arises due to somatic loss-of-function mutations in phosphatidylinositol glycan anchor biosynthesis class A gene (PIGA) in haematopoietic stem cells (HSC). This can lead to an absence/significant reduction of GPI anchored proteins which serve as scaffolding for several regulatory molecules on the cell surface, including those keeping the complement system in check. The two cell surface proteins of significance for the pathology of PNH are CD55 and CD59.

In normal blood cells, CD55 and CD59 protect the cells from being destroyed if the complement system (part of the innate immune system) is activated to fight an infection, whereas their absence leads to uncontrolled/continuous complement activation that results in the destruction of the red blood cells (haemolysis)[1,2]. Depending on the clinical manifestation of the disease there are three different subcategories: classic PNH, PNH in the setting of an associated bone marrow disorder, and subclinical PNH[3].

A complement inhibition therapy is considered the best approach against PNH, since complement inhibitors inhibit classical, lectin, and alternative mediated haemolysis[4]. To improve life expectancy, intravascular haemolysis (IVH) must be controlled (IVH). If left untreated, IVH can lead to thrombosis (blood clots) and disabling symptoms such as fatigue, intermittent episodes of dysphagia (swallowing difficulties), abdominal pain, and haemoglobinuria (presence of blood in the urine)[1,5]. Despite reduction of thrombotic events and increased life expectancy by blocking IVH, many patients are still anaemic and have persistent impairments of their QoL because of ongoing extravascular haemolysis (EVH) which can contribute to persistent anaemia and even transfusion-dependence.

The estimated prevalence of PNH is between 5 and 20 people per million, but there is a lack of clarity regarding the actual number of people living with PNH globally, which may be underestimated due to underdiagnosis caused by its rarity, lack of awareness, and testing[6,7]. A retrospective cohort study in the U.S. using data from 30 million patients found that an incidence rate for PNH of 5.7 per million and a prevalence of 1.76 cases per 100,000 individuals[8], whilst a study in the UK with 3.8 million patients reported an incidence rate of 3.5 per million and a prevalence of 3.81 per 100.000[9]. In Australia, the true prevalence and incidence of PNH remains unknown. Clinicians estimate that there may be up to 170 patients that would require treatment[10].



In the Nordic countries, the incidence and prevalence are more accurate due to the centralisation of the diagnostic centres and unique systems of database records. The total population of the study regions was 13.2 million and the mean incidence of newly detected PNH cases was 2.33 per million/year[11]. PNH can appear in patients of any age, but most are diagnosed with PNH in their 30s and 40s, with a median age of diagnosis in their mid-30's[8]. There are no apparent differences between the incidence of PNH in different geographic regions or ethnicity, although it is believed to occur slightly more frequently in women than in men[12].

ii. Objectives (Why PNH? Why A Global Policy Consensus Paper Now?)

Historically, median survival for people living with PNH has been between 10 to 15 years from diagnosis but this has improved to near normal because of the first complement inhibitor therapy which was approved in 2007. Nevertheless, still today, people living with PNH report unmet medical needs which have a significant impact on their daily lives. As research in PNH is evolving and therapeutic benefits are improving, health policy must adapt to the progress of science. Besides treating clinical manifestations and preventing major complications, the community has started to set new goals in the management of PNH towards further improvement of the QoL and better living with PNH.

This global policy consensus paper lays out the challenges faced by people living with this life long, ultra-rare disease called PNH when accessing care and adequate treatments. It spotlights the gaps across global policies accompanying the patient journey, from presentation of symptoms to diagnosis, to access to treatment and care, as well as the impact on mental health. Partnering4PNH proposes constructive solutions to these challenges while also gathering political support for them, at a time where the whole of Europe and global framework is changing. It should be acknowledged that these recommendations serve as a roadmap for further development of national policies.

iii. About Partnering4PNH (Members, Approach)

Partnering4PNH is a global multistakeholder policy initiative which brings together PNH experts with a range of perspectives. Its members are representatives of patient associations, clinicians, nurses, and industry from different European countries such as the UK, Spain, Ukraine, but also from Canada and Australia. Partnering4PNH has two political Co-Chairs, who are the Members of the European Parliament (MEPs) István Ujhelyi (Hungary, Socialist and Democrats) and Stelios Kympouropoulos (Greece, Christian Democrats). The Partnering4PNH initiative is organised and funded by the Swedish Orphan Biovitrum AB (Sobi), whilst the Secretariat is led by Evoke Incisive Health.

This policy consensus paper is the result of a combination of desk research and interviews with specialist medical practitioners, patient group representatives, and policymakers. It is also based on published resources, including position papers, clinical guidelines, and information provided by patient groups. Furthermore, this paper reflects the consensus of the Partnering4PNH expert group based on several discussions and prioritisation exercises to support consensus development. The outcome of this prioritisation supported the development of the policy recommendations and are captured in the annexes of the paper.

Section 3. Diagnosis Journey and Treatment

i. Diagnosis Journey

Case reports of PNH date back to the 1880s, but the term was first introduced by Enneking in 1925. The first diagnostic test for PNH was developed in 1954, which is known as the Ham test[7]. Due to poor disease awareness and heterogeneity of presentation, the diagnosis journey is long: an online survey of 163 people living with PNH indicated that diagnosis takes 2 years on average (more than 5 years for 24% of patients) and requires consultation with different physicians (more than 5 physicians for 38% of patients)[13,14]. The challenge of diagnosing and caring for people living with PNH is increased in geographically large countries such as Australia and Canada, as expertise centralisation is not possible to the same degree as in smaller countries[15].

Most people living with PNH present to a primary care physician (PCP) with symptoms that may include fatigue, dark urine (haemoglobinuria - which is haemoglobin in the urine - is not to be mistaken with haematuria - which is the presence of blood in the urine), anaemia, dyspnoea (shortness of breath), gastrointestinal issues, or thrombosis (blood clots)[14,16]. PCPs may eliminate common diagnoses based on patient symptoms before eventually referring them to a haematologist. It is estimated that around 15% of people living with PNH present directly to emergency medicine physicians (for example following a thrombotic event such as a stroke) and will subsequently undergo a similar process of eliminating common conditions before referral to a haematologist[17]. There are several conditions which exist simultaneously, including iron deficiency anaemia caused by the ongoing haemolysis and bone marrow failure conditions, such as aplastic anaemia (AA) or myelodysplastic syndrome (MDS), which make a PNH diagnostic challenging[18]. Consequently, before a haematologist referral, some patients are referred to urologists (23%) or mental health specialists (11%)[14]. See Figure 1

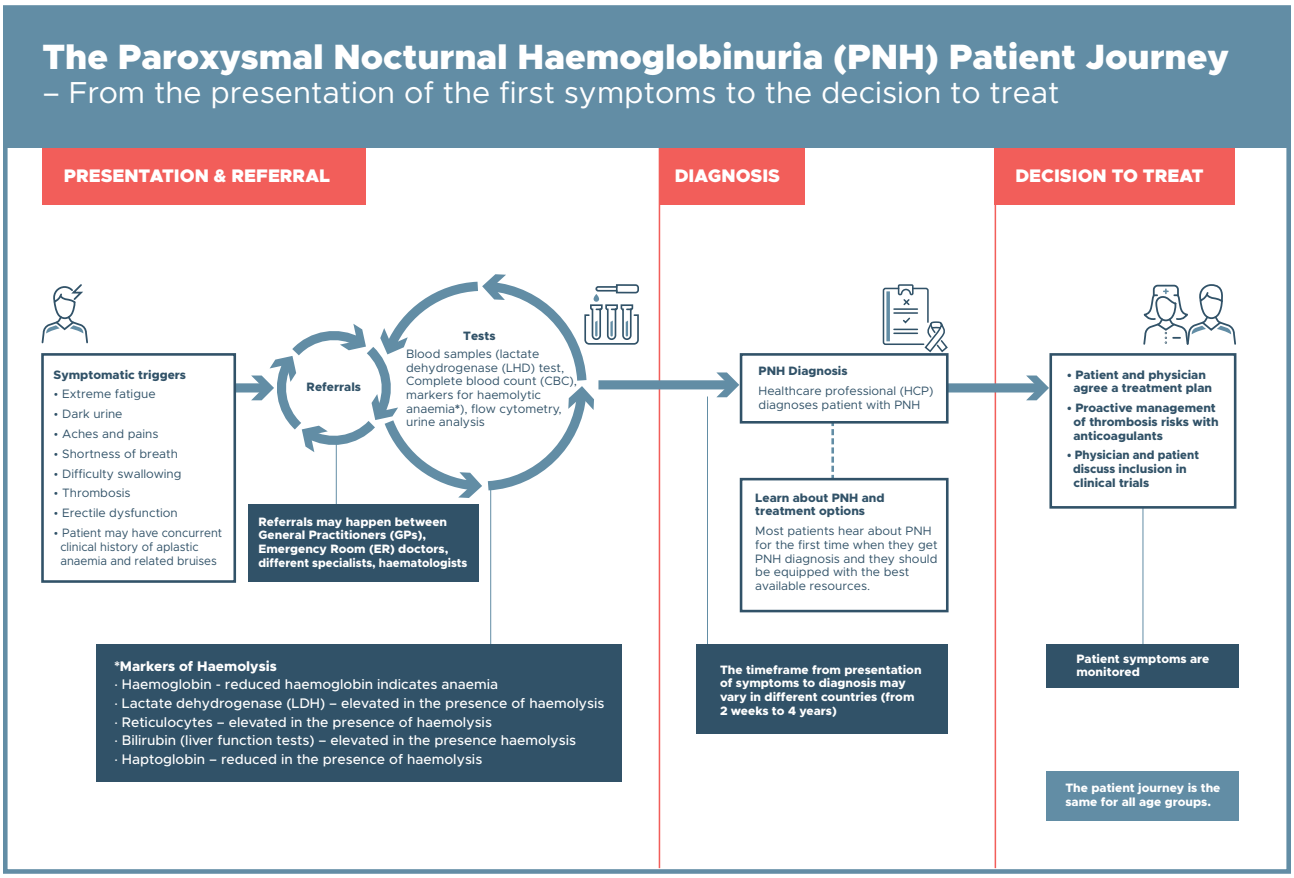


Figure 1: The PNH Patient Journey – From the presentation of the first symptoms to decision to treat

If PNH is suspected and certain clinical criteria are met (e.g., unexplained haemolysis), PNH diagnosis is confirmed with a flow cytometry which determines the proportion of blood cells affected by PNH[16,19].

Diagnosis of paediatric patients typically follows a similar pathway. However, the rare incidence and non-specific clinical presentation create additional challenges to diagnosing PNH paediatric cases, resulting in higher rates of misdiagnosis and delays.[20,21] In addition, the extended diagnostic journey has a negative financial and emotional impact on the wellbeing of people living with PNH and their carers[17].

ii. PNH Management

a. Countries without complement inhibition

Following a confirmed PNH diagnosis, treatment is initiated by the haematologist to prevent life-threatening thrombosis[16]. Currently, there is a global discrepancy between countries that have PNH clinical guidelines and authorised treatments and those that have none, such as Asian countries (including India), Latin America, and certain European regions (see Annex 1)[22].

For patients with subclinical PNH (12% of PNH patients[23]), identification of the clone is typically carried to identify any bone marrow failure syndromes (e.g., aplastic anaemia, myelodysplastic syndromes). Specific treatment for subclinical PNH is not required, but patients may require therapy for the underlying disease, including immune suppression and transfusion support[24].

Allogenic haematopoietic stem cell transplantation (HSCT; bone marrow transplant) is a potentially curative treatment option for people living with PNH due to its ability to eliminate PNH clones[16]. However, in most countries transplant is only considered in most severe cases, typically for patients with other bone marrow disorders, such as aplastic anaemia (18%[23]). The substantive mortality implications associated with transplant procedures must be considered[25].

Sustainable access and availability of treatment is a common problem to all rare diseases, including PNH. In countries where treatments are not available or where access to treatments and expertise is very limited, people are still dying of PNH. Improving the survival chances of people living with PNH should be the priority in those countries.

b. Countries with complement inhibition

In countries with PNH clinical guidelines and authorised treatments, disease management tends to be broadly similar. A recent systematic review showed consistent recommendations across Australia, Argentina, Germany, Italy, Japan, Turkey, Spain, Switzerland, the UK, and the US[26,3]. Although there are treatment guidelines developed in most countries around the world, many have not been updated in the last five years[26] (See Annex 1). As new treatments get approved, the medical community should initiate updates of these national guidelines.

For patients with classical PNH (70% of PNH patients), targeted therapy to inhibit terminal complement activation via C5 inhibition is recommended. Additional treatment options may include blood transfusions, haematinic support, and analgesia for smooth muscle dystonic complications (e.g., abdominal pain, dysphagia). In addition to C5 inhibitors, other novel therapies that inhibit the more proximal complement targets, such as C3, are available or under investigation[27].

Around 25-50% of patients on C5 therapies develop C3-mediated EVH[27]. This inadequate haematological response is driven by an uncontrolled activation of the proximal complement, which leads to an opsonisation of red blood cells (RBC) with C3 fragments[27]. This can have a significant clinical impact on the patient, and in fact, EVH is considered the main cause of residual anaemia and transfusion dependency in patients previously treated with C5 inhibitors[27]. Treatments targeting complement proteins involved in the phases of complement activation (upstream C5) may counteract the uncontrolled C3 activation and thereby address both IVH and EVH[27].

Section 4. What Are The Remaining Unmet Medical Needs And Can They Be Met?

i. Remaining Unmet Medical Needs in PNH

PNH is associated with a significant clinical and economic burden[28]. Most used instruments for disease burden assessment are non-PNH specific and include the Functional Assessment of Chronic Illness Therapy Fatigue scale for chronic diseases (FACIT-Fatigue with scores from 0 to 52, higher scores indicating less fatigue), or the oncology-specific European Organization for Research and Treatment of Cancer Quality-of-Life (QoL) Questionnaire-C30 (EORTC QLQ-C30)[29], although some PNH-specific assessment tools are emerging but require clinical validation[30,32]. Left untreated, people living with PNH are at increased risk of life-threatening complications and experience a significant QoL impact with high frequency and severity of daily symptoms. As such, the key sources of burden for PNH patients include:

- **Risk of thrombosis**: A burden of disease study in Europe (n=71) reported that 38% of patients had experienced at least one thrombotic event in their lifetime [28,33].
- **Transfusion risks**: The need for blood transfusions is quite common for people with PNH due to the high prevalence of chronic anaemia[28]. Transfusions are associated with a risk of reaction, development of antibodies and iron overload (21% of patients). Moreover, as transfusions only increase the haemoglobin level acutely, patients are left with long periods of suboptimal haemoglobin level[34].
- **Severe fatigue**: The most common symptom in people living with PNH despite C5 therapy. Schrezenmeier et al. (2020) reported an average FACIT-Fatigue score of 34 for PNH patients vs. 44 across the general population (a difference of five points or greater is considered clinically important)[35,36]. In addition, data from the International PNH Registry found that people with PNH who had experienced fatigue were significantly more likely to be hospitalised than those who had not (~25% vs. ~15%; $P < 0.01$)[37].
- **Economic impact**: Both at an individual patient level, due to an impaired ability to work, and at a healthcare ecosystem level, given the significant requirements for medical interventions (average of 16.7 healthcare visits, 6.7 specialist visits, 1.9 hospitalisations events, and 0.5 emergency department visits per year) as well as possible blood transfusions and annual treatment costs[28].

a. Impact of Persistent PNH Symptoms on QoL and Work Productivity

In alignment with international guidelines, the primary goal in the management of PNH is to improve survival and manage haemolysis and risk of thrombosis. C5 inhibitors have delivered significant improvements for the patients as the first agents specifically approved for PNH, normalising life expectancy and addressing IVH symptoms[38,39].

However, retrospective analyses of C5 inhibitor-treated patients found that up to 36% of patients remain transfusion-dependent and 72% had residual anaemia[40,41]. In addition, only 10% of C5 inhibitors-treated patients had a complete response after 12 months of treatment (defined as no transfusion requirement, normal haemoglobin levels, lactic dehydrogenase (LDH) levels <1.5 times the upper limit of normal, and reticulocyte count ≤150,000 μL-1)[41] and around 25-50% of patients on C5 inhibition develop C3-mediated extra-vascular haemolysis.

A recently published cost effectiveness analysis of a C3 complement inhibitor was associated with an increase of 1.75 QALYs (Quality Adjusted Life Years) per PNH patient compared to C5 complement inhibitors[42]. It is a growing consensus that the burden and severity of this debilitating symptom may represent a critical component of treatment and management among these patients.

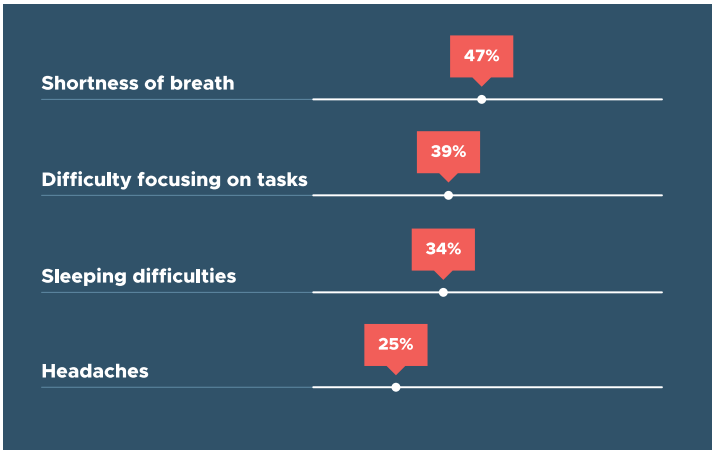
This fatigue is also often associated with other symptoms and an ethnographic study concluded that 21 of 27 patients raised neurological (e.g., brain fog) and psychological (e.g., depression) symptoms as a significant burden that is not given enough attention by treating physicians.

Other common symptoms reported by C5 inhibitor-treated PNH patients included:

Difficulty focusing on tasks and sleeping difficulties were more prevalent when patients had been receiving treatment than when they had initially received a PNH diagnosis. Additionally, 49% of treated people with PNH reported suffering with depression[28].

"Many patients mention fatigue as one of the main struggles they face despite receiving a treatment. Fatigue has an impact on patients' ability to work, relationships, and hobbies, affecting both their professional and personal lives. The impact of the disease on people's quality of life is one of the most difficult aspects to assess in PNH. Physicians struggle to discuss this topic as there are currently no treatments widely available for fatigue"

Olena Wagner, Chair, PNH Ukraine



To further quantify the humanistic burden of PNH, for example on work productivity, two studies were conducted using the Work Productivity and Activity Impairment (WPAI) questionnaire, which is a psychometrically validated and designed for adaption to specific diseases.[43,44]

These studies have analysed the work productivity of C5 inhibitor-treated patients following the WPAI methodology and found that 45-55% of patients were, at the time of the study, in paid employment. Of these, 70-80% were experiencing an impact on their work productivity due to PNH and 30-50% of patients had missed working hours in the week prior to completing the survey, suggesting a high indirect economic impact at both individual and societal levels.[28,45]

The evidence from these studies clearly shows that the QoL and work productivity of people living with PNH is still considerably impacted. In addition to this, EU wide and national actions should be undertaken to recognise the health specificities of people living with PNH and to design social systems that account for these conditions in the labour market (e.g., work flexibility, diverse employment opportunities).

b. Impact of Treatment on The Daily Lives of People Living With PNH

Considering that the median age of PNH diagnosis is mid 30s and the associated treatment burden, people living with PNH face many restrictions. They are often tied to a hospital or treatment centre to receive their treatment which can translate into long journeys and further impact to their lives and finances.

Some of these restrictions can be improved by treatments with longer halflives, and/or administration at home (e.g. subcutaneous injections).[46,47]

Recently patients that have selfadministered treatment at home have reported a positive impact on their QoL, as they no longer have to plan their lives around hospital or treatment centre visits:

The psychological aspects of having a chronic illness at a young age, as well as the potential limited earning capacity for life may be affected. Patients also have considerations including family planning, which are more complex with a chronic disease.

For children diagnosed with PNH, impact on education and the burden of disease compared to their peers is highly significant.

"The treatment has changed my dependency on having to go to the hospital since I administer it myself. That means that the doctors trust that I am administering it well. In my daily life, it translates into having to request less time off from work and being able to travel in Spain as it is easy to organise between weekly doses."

Spanish PNH Patient

"Patient self-management is good next step especially with subcutaneous therapies. Brings responsibility back on to the patient, flexible infusion timing, and increased ease of travel to remote destinations. However, many patients express preference to keep illness management separated from home."

Michael Brown, PNH Clinical Nurse Consultant, The Royal Melbourne Hospital, Australia

"The treatment changed my life in terms of health, everything has been much better since, but at the cost of less freedom. In my case, I have reached a good format of visits and treatment during the week, but only because I work part time. I see travelling to other countries as something very complicated, not only because of the treatment but also because of the difficulty to transfer my entire patient file."

Spanish PNH Patient

ii. What Constitutes Improvement in PNH?

a. Where Are We going? The Journey To Set New Treatment Goals for PNH

For many people living with PNH, the fragility of life and the prospect of death was apparent before the approval of the first complement inhibitor treatment in 2007. In the last 15 years, research into PNH has increased significantly and will continue to increase, allowing physicians to provide a personalised approach to treat PNH, both by targeting the complement pathway "upstream" from C5, addressing extravascular haemolysis, and the options of orals, subcutaneous or longer acting IV therapies.[33,48]

Whilst diagnosis is gradually becoming more homogenous across various countries, access to complement inhibitor therapies still varies around the world, especially at regional level. Given these multi-dimensional challenges, it is key that global and national PNH communities (clinicians, academia, patient advocacy groups, patients, and their caregivers) continue to advocate for the lives of people living with PNH in order to maximise current and future therapeutic benefits according to individual needs.[27,48] As new treatments get approved, the medical community should initiate a re-evaluation of the disease, as well as the treatment response criteria in medical guidelines, in order to identify patients who may benefit from a patient-centric tailored approach and address the unmet medical needs.

> **"People living with PNH are keen to access treatments that offer greater self- management. With C5i near normalising life expectancy we can now address the remaining unmet medical needs for patients including quality of life and burden of treatment."**
>
> **Dr Morag Griffin, Haematologist PNH Specialist, Leeds Teaching Hospital, United Kingdom**

b. Understanding PNH Beyond the Lab Result

According to international clinical guidelines, people living with PNH must undergo regular clinical and laboratory assessments to monitor possible changes in disease presentation.[27] It is common for patients over time to understand their condition and become experts of their own disease, including their symptoms and blood results.[49]

Among patients with cancer, who also have anaemia and fatigue, there is substantial evidence which demonstrates that increased haemoglobin levels are associated with clinically meaningful improvements in QoL. These results are gradually also being confirmed among patients with PNH, which show that the management fatigue is correlated with meaningful improvements in clinical and haematological parameters across PNH patients, including haemoglobin levels, absolute reticulocyte count, and indirect bilirubin levels.[37,50] In fact, the largest reduction in fatigue (11.3-point improvement in FACIT-Fatigue total score) has been seen in patients with a significant increase in haemoglobin levels (>2g/dL).[50] A significant reduction in fatigue (9.3-point improvement in FACIT-Fatigue total score) has also been reported in patients with a decreased absolute reticulocyte (> median 70x109 cells/L) and indirect bilirubin levels (Median 7.6 umol/L).[50]

In this regard, an instrument for measuring aplastic anaemia and PNH-specific QoL (QLQ-AA/PNH) which has shown good internal consistency (e.g., Cronbach's alpha of the fatigue scale was 0.88) may soon be used to provide more tailored QoL measurements for people with PNH.[30] Furthermore, a self-reporting symptom

questionnaire (PRO) with 30 questions has been developed to capture both the physicians and patients' perspective on AA and PNH. The resultant ratings were consistent with previous studies where patients consider symptoms associated with their day-to-day health status whilst clinicians focus on unfavourable clinical outcomes (such as emergency visits).[32] A prioritisation exercise with the members of Partnering4PNH confirmed among the top three priorities the need to establish in the short-term common definitions and measurement tools for overlooked symptoms in PNH, such as severe fatigue (see Figure 2).

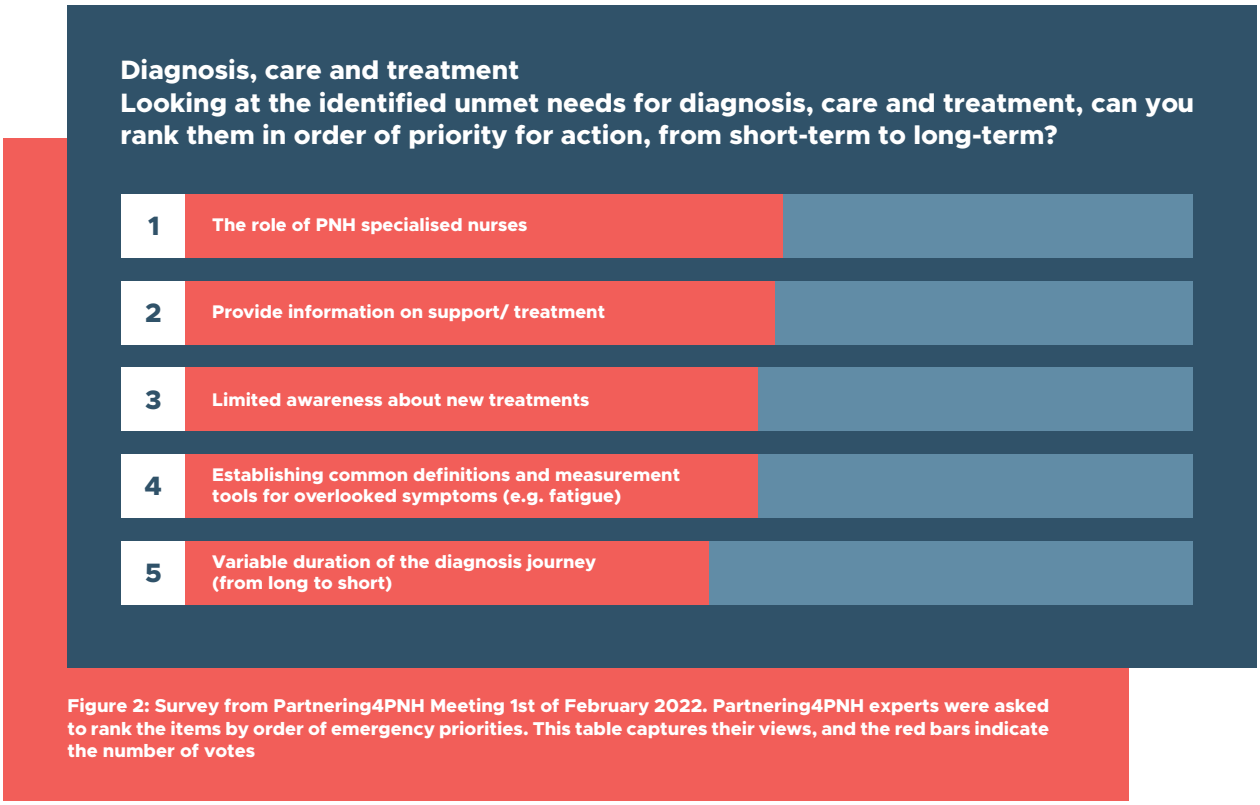


Figure 2: Survey from Partnering4PNH Meeting 1st of February 2022. Partnering4PNH experts were asked to rank the items by order of emergency priorities. This table captures their views, and the red bars indicate the number of votes

Section 5. On The Frontline to Address PNH Unmet Needs

i. The Key Role of Specialist Haematologists in PNH Patient Care

Despite improvements in PNH management, diagnosis is still challenging for physicians.[15] In addition, the expert group of Partnering4PNH believes that after a diagnosis, people living with PNH often receive unclear information on how to manage their disease.

A potential reason for this might be a lack of awareness and knowledge of PNH-specific symptoms among physicians.[15,51]

Although specialist centres provide regular education on PNH diagnosis and management [52], PNH should be an integral part of a haematologist's professional curriculum.

"In Canada, there is a lack of awareness of the disease amongst HCPs. Education for HCPs needs to be prioritised as it still takes a long time for many patients to be diagnosed with PNH. Some haematologists do not understand the disease, and this should be the starting point in terms of education needs."

Cindy Anthony, Executive Director, Aplastic Anaemia and Myelodysplasia Association of Canada, Canada

Considering the rarity of this disease there are also few PNH experts who can raise awareness and educate fellow HCPs and haematologists.[16] For example, all Canadian PNH experts work across thirteen academic hospitals located in the Central and South of the country and, in the UK, only two PNH Specialist Centres, supported by seven outreach clinics, are available for PNH patients.[52,54] In Australia, where outreach clinics are less viable to establish due to country size, haematologists often utilise telehealth to monitor the health of their patients.

ii. The Key Role of Nurses in PNH Patient Care

"It is essential for haematologists and other HCPs involved in the management of PNH to educate patients but also their caregivers, on how to live with and manage PNH. It is also important for HCPs to inform them of the available resources available and put them in touch with the relevant patient association(s) and any existing support groups (including any patient and mentor programmes)."

Dr Christopher Patriquin, Haematologist PNH Specialist, Toronto General Hospital, Canada

Together with haematologists, PNH nurses play a key role in the care and wellbeing of PNH patients. As frontline healthcare professionals they provide support across the entire path of PNH management – from investigations and diagnosis, through to treatment and palliative care and across the lives of PNH patients.[55]

Nurses evaluate patients with suspected or diagnosed PNH, monitor symptoms of fatigue or signs of bleeding or thromboembolism. For diagnosed patients, nurses are involved in the delivery of all supportive treatments.[55] As such, nurses must stay informed with the latest disease information and management strategies.

As part of their educational role, PNH nurses often liaise with patient groups for information exchange (links to websites and videos explaining the disease and the treatments) and connect those patients with an early diagnosis to specialised patient groups and/or patients who have been living with the disease for a longer time.[55]

Furthermore, PNH nurses play a critical role in empowering the caregivers for example by educating them to track potential changes in the patient´s condition, which can enable a rapid investigation and management of the symptoms. Nurses find it important to work with the caregivers of people living with PNH especially when making critical decisions.[55]

Finally, PNH nurses play an important role in supporting HCPs understanding of the disease burden and its impact on the QoL for people living with PNH. At the national PNH service in the UK and RMH PNH service in Australia, PNH nurses have an open-door policy for patients and HCPs where they can ask questions (also via telephone/email) on the disease and its management etc. In England, PNH specialised nurses have established nurse forums that are dedicated to knowledge exchange and provide educational training. The RMH PNH service in Australia has also tried to establish national PNH specific nursing forums, but there are challenges to formalise especially since the number of PNH patients receiving care in the treating centres is small.

"Nurses are often considered a primary source of support for patients when dealing with haemolytic events, infections, or side effects from medications. They also play a key role in sharing information with patients on the variety of symptoms associated with a diagnosis of PNH, including severe fatigue."

Louise Arnold, PNH Specialist Nurse, Leeds Teaching Hospital, United Kingdom

In Canada, the mentor system set up by the Canadian Association of PNH patients encourages people with PNH to openly communicate and share their feelings/ experiences with each other. Those with more experience can educate newly diagnosed patients on what to expect, how to live with PNH, how to adjust to treatment, and to provide comfort. The interaction between patients changes when they are organised in groups and can provide their expertise to others."

Barry Katsof, President and Founder, Canadian Association of PNH Patients, Canada

iii. The Role of Patient Groups in Supporting People with PNH

Patient groups play a crucial role in informing and providing support to other patients. They help people living with PNH take ownership for their own care journey. Connecting newly diagnosed patients with patient organisations and patients with more experienced peers or "buddies" is a valuable model of sharing information. Even if there are some written resources available for people living with PNH, there is a lot of educational value in patients talking to each other.

Furthermore, the Canadian Association of PNH Patients has recently developed a guide called "Better living with PNH".[56] The guide focuses on exercise, nutrition, and mindfulness to help people with PNH understand how to better cope with PNH and live with the disease. The guide can help patients adopt a healthy lifestyle and improve their QoL.

Patient organisations also play a role in providing information to healthcare professionals and can be involved in policymaking. It is important to organise and develop the correct systems to share information and tools with patient, healthcare professionals and policy makers.

Section 6. Policy Recommendations

Recommendation 1. Increase awareness on PNH

Despite PNH seriousness, there is still a lack of awareness that often results in an extended diagnosis journey, misdiagnosis and underdiagnosis. An online survey of 163 PNH patients demonstrated that a PNH diagnosis takes (2 years on average, and more than 5 years for 24% of patients) and can require consultation with several different physicians for some patients (more than 5 physicians for 38% of patients).[14] The expert group of Partnering4PNH believes that earlier diagnosis improves patients' outcomes, can reduce the negative financial and emotional impact of the disease and assure the sustainability of healthcare systems.

- Considering how unspecific PNH symptoms are, Partnering4PNH believe that building awareness and understanding of PNH among HCPs, but also policy and decision makers is needed. Centralisation of rare disease knowledge and patient oversight via the reference centres like those put in place in Europe, would be significantly reducing the time between the first presentation and final PNH diagnosis.

- Centralized oversight of patients with decentralised care management could further ensure consistent care and better management of needs across the country and irrespective of location. By enhancing public and private research in rare haematological disorders, governments can build regional or national hubs to enable further accumulation of knowledge and expertise, which could ultimately also support better care for people living with ultra-rare diseases such as PNH.

- Furthermore, the use of targeted PNH biomarkers (e.g., flow cytometry, LDH, haemoglobin level) are necessary to not only confirm a diagnosis but also to inform a management strategy given the diverse clinical manifestations of this disease

- Lastly, international organisations such as the International PNH Interest Group (IPIG) play a key role in advancing the knowledge about the disease, optimal care and treatment for PNH patients. For example, the PNH registry collects data on the natural history of PNH and aims to optimise clinical decision and enhance understanding of PNH and its treatments. Data collected from every PNH patient are invaluable in providing insight into this rare disease but also raising awareness within the PNH community. Currently the PNH Registry includes data from over 5,000 volunteer patients worldwide.[57]

Recommendation 2. Reduce inequalities and expedite access to treatment

The low prevalence, lack of awareness and understanding of PNH, is coupled with significant barriers for access and availability of treatments. The willingness among decision makers to invest in treating ultra-rare disease patients also varies significantly across countries which is reflected in the heterogenous access journey for orphan drugs, from regulatory approval to reimbursement. Whilst acknowledging that the issues pertaining to access and reimbursement require multi-dimensional solutions, including cross-country collaborations, Partnering4PNH encourages the use of value assessment frameworks for rare diseases, as an immediate first step to inform health decision making and expedite access.

- One key access milestone during a health technology assessment is the evaluation of the degree of evidence of the treatments at the time of the reimbursement approval of new treatments. Demonstrating relevant clinical benefit and value for money for orphan drugs is difficult when based on conventional Health Technology Assessment (HTA) frameworks. HTA bodies need to consider the indirect costs or non-health related benefits, such as relieved caregiver burden, improved mental health, and ability to return to work in their decisions. Most patients are diagnosed with PNH in their 30s and 40s, with a median age of diagnosis of mid 30s. Recent Work Productivity and Activity Impairment (WPAI) surveys indicate that less than half of respondents on C5i are employed suggesting a high indirect economic impact at the individual and societal level. Moreover, in these surveys 30-50% of PNH patients reported absenteeism in the past 7 days and 70-80.3% reported decreased productivity due to their disease. By failing to consider the indirect costs, HTA bodies may undervalue new treatments thus limiting the possibility for many patients to significantly improve their life.

- Pooling and centrally collecting data are key to understanding the disease and inform regulatory and national HTA bodies decisions. For example, in 2017, the European Commission established the European Reference Networks (ERNs) – virtual networks of healthcare providers – to facilitate, among others, research on complex or rare diseases that require highly specialised treatments.[56] To address the fragmentation of rare disease patient data contained in hundreds of registries across Europe, EuroBloodNet created ENROL, the European Rare Blood Disorders Platform as an umbrella for new and existing registries in Rare Haematological Disorders.[58,59] Whilst such efforts to centralise data might take longer to set up compared to national disease specific registries, such platforms like ENROL have the potential to provide health authorities with cross-country epidemiological and disease burden data to improve health planning.

- The use of real-world evidence (RWE) from national or international disease registries (such as the International PNH registry) can help gain a better understanding of patient's health and experiences' and potentially confirm the value of new medicines. Clear guidelines for accepting, analysing, and interpreting RWE studies for regulatory purposes and health technology assessments should be created at the global or EU level. EU initiatives such as DARWIN EU (Data Analysis and Real-World Interrogation Network) and the new regulation on EU HTA can foster a transparent and cohesive environment and help expedite patient access. Equally important is the need to define simpler European or national legal frameworks for obtaining patient consent for sharing and using their real-world data.

Recommendation 3. Improve understanding of PNH through the use of specific HRQoL/PRO measurements

To support adoption and use of new therapies that address the unmet needs of people living with PNH, measurement and collection of QoL data is vital to understand the holistic impact of the disease. The frequency and severity of specific symptoms must be captured from a physical, psychological, functional, and social perspective with a disease-specific approach.

- Currently, PNH disease burden is assessed via non-disease specific instruments such as the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-Fatigue) scale for chronic diseases, or via oncology specific instruments such as the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-C30 (EORTC QLQ-C30). A suitability assessment of these scales concluded that they were relevant and adequate, although more could be done to tailor them to the specific burdens faced by people living with PNH. Considering the rarity and heterogeneity of PNH symptoms such HRQoL or PROs scales need to be considered by HTA bodies in their assessments of innovative treatments. Furthermore, Partnering4PNH recommends that specific PNH HRQoL questionnaires such as the QLQ-AA/PNH developed by Niedeggen et.al or the self-reporting questionnaire (PRO-AA/PNH) developed by Weisshaar et.al. are globally validated, for e.g. in the context of PNH registries and used to inform future decisions in treating PNH.

- Although there are some PNH symptoms that patients can detect such as abdominal pain or dark-coloured urine (haemoglobin in the urine), there are many other overlooked signs which are linked with haemolysis and elevated risk of thrombosis. The expert group of Partnering4PNH believes that collecting data on persistent symptoms such as fatigue or other cognitive complications via specific PNH measurements can contribute to addressing the remaining unmet medical and patient needs.

Recommendation 4. Empower patients and their caregivers in decision making

Health literacy and capacity-building, shared decision-making and support to self-management are all components of patients' empowerment which help build patient-centred healthcare systems. Whilst recognising that long term advocacy is needed to formally incorporate the experiences and needs of patients in the decision process, Partnering4PNH supports the education and empowerment of PNH patients as a key element for better outcomes. The expert group of Partnering4PNH believe that it is essential for haematologists, nurses, and other HCPs involved in the management of PNH to educate patients but also their caregivers, on how to live with and manage PNH. It is also important for HCPs to inform them of the available resources available for them and put them in touch with the relevant patient association(s) and any existing support groups (including any patient and mentor programmes).

- Empowerment has implications for both the overall PNH community and the individual patient. As for the latter, Partnering4 PNH encourages the establishment of a mentorship system. This peer-to-peer support can deliver added value in terms of sharing of information, education of patients on their disease and unmet health needs. The objective of this approach is to foster peer education so that patients can actively make informed decisions about their own care.

- As for the PNH patient community, when it comes to shared decision-making, Partnering4PNH believes that the full professionalisation of patient organisations is crucial e.g. by having medical representation on patient boards. The establishment of PNH patients' national and inter-country academies, with the involvement of both HCPs and patient organisations from other countries can help in fostering continuous education and exchange of best practices, for example shared decision-making tools, use of digital applications). Moreover, through the exchange of information within the PNH academies, patients can discuss holistic approaches to manage the disease and ways to improve the quality of their lives.

- Moreover, specific trainings should be provided on reinforcing communication skills from patients' sides (for example encourage them to report symptoms and adverse events) and provide psychological support to patients and caregivers.

Recommendation 5. Strengthen the role of nurses in PNH patient care

PNH is a lifelong ultra-rare disease and nurses play a crucial role for PNH patients throughout the pathway of care. Currently, many people living with PNH are supported by non-specialised nurses, which in acute situations raises unforeseen challenges.

- PNH specialist nurses are extremely valuable but also rare. However, a PNH specialisation could be offered to nurses as an opportunity for career development. The expert group of Partnering4PNH believe that regular educational programmes should be offered to haematology and PNH - specialised nurses which can include information on the latest disease management strategies, how to administer prescribed medications, information on potential side effects of therapies and necessary patient monitoring. A formal nurse training curriculum should be developed at a national level to ensure that PNH symptoms are properly understood and detected.

- The expert group of Partnering4PNH believe that a national core PNH network of nurses, which could support general haematology nurses, would be extremely valuable especially when dealing with difficult cases at a national level and in cross-country emergencies. In countries with no centralised care, this network could bring significant value to patients and the healthcare systems.

- PNH Specialist nurses should be involved in the trainings of HCPs, for example through PNH academies or act as contact points to disseminate knowledge. Nurses can play a key role in supporting HCPs understanding of the disease and the day-to-day burden of the symptoms on patients and their caregivers.

Recommendation 6: Build a more resilient ecosystem for rare disease research and innovation

The past 20 years of advancements in innovation for rare diseases in Europe are directly linked to the establishment, in the year 2000, of the European Orphan Medicinal Products (OMP) and Paediatric Regulation. People living with a rare disease, could only access eight treatments before the adoption of the EU OMP Regulation. This number has increased to almost 190 and it also includes treatments that people living with PNH can access today. However, to this day, 95% of rare disease patient still lack a viable treatment, while the remaining 5% are likely to face significant hurdles in the patient journey. We believe that the EU OMP regulation is a good illustration of how a well-designed legal framework can encourage innovation within and beyond Europe.

In Canada, the length of time from regulatory approval to reimbursement varies significantly across the different Canadian provinces. Furthermore, not all nationally approved rare disease drugs are publicly reimbursed across the different provinces, which as a result impacts the time and availability of these treatments.[60]

In Australia, the orphan drugs policy was set up in 1997. It aims to ensure the availability of a greater range of treatments for rare diseases. However, the healthcare financing system in Australia hinders the delivery of orphan drugs to patients. The Australia Pharmaceutical Benefits Scheme provides subsidies to enhance accessibility of drugs, whilst the Australian Health Care Authorities are currently discussing the inclusion of orphan drugs in the scheme.[61]

In order to expedite access to these medicines, regulators, HTA bodies, payers, patients and industry need to work closer in order to shape the future of rare disease therapies for the next 20 years. Therefore, it is key to work towards improving regulations which build upon elements of success similar to the EU OMP Regulation and create a more resilient ecosystem for future rare disease research and innovation.

- The policy framework should holistically support research and innovation in rare diseases, thus building on existing initiatives like the European Reference Networks (ERNs). Integrated information management systems that support faster and smoother collaboration among clinicians, researchers, national institutions, patients, and industry are essential for an innovative environment that fosters innovation in rare diseases. In this sense, the European Health Data Space offers the perfect opportunity to harness the full potential of data and information for the benefit of people living with a rare disease, like PNH. By making secondary use of data and by ensuring that national disease registries are interoperable, the EHDS has the potential to unleash a new path for research and innovation in rare diseases in Europe and beyond.

- A thoughtfully calibrated incentive framework constitutes the foundation to continue to attract research into areas with no or limited treatment options. Without a predictable model to protect original research (such as data and marketing protection) innovation for ultra-rare diseases such as PNH would become increasingly difficult, ultimately impacting those who are most in need of treatments. One licensed OMP does not equate to the alleviation of all unmet medical needs.

- Ultimately intensifying research efforts to bring new innovation can positively influence market dynamics with improved outcomes for patients over time. Creating a solid ecosystem for future innovation to flourish, whilst balancing the financial and fiscal sustainability of healthcare systems in Europe and around the world is a shared responsibility that requires commitment and partnership from both the private and the public sector.

Conclusion

Research around PNH has made headway in the last decade, encouraged by regulations in Europe and around the world, which supported the development of new treatments which can improve life expectancy to near normal and the QoL for people living with this condition. However, as we have consistently shown throughout this paper, PNH still has negative socio-economic impacts on patients and their caregivers throughout their whole lives.

While the first, important step of Partnering4PNH comes to light through this global policy consensus paper, we can take stock of what the experience of Partnering4PNH has meant until this moment. This collaborative group of various experts from Europe, Canada and Australia came together to share experiences of PNH – on what it means to live with it, to provide care to those who are affected by it, on the differences that exist across these geographies, particularly in regards to the different levels of the unmet medical needs – and it reminded us that none of us, no matter the role we play in the disease journey, is an island entire of itself. The simple fact of sitting around a – often virtual – discussion table is a powerful way to ignite change. Working together and promoting constructive conversations across different functions and geographies is the best way to make the leap from problem to solution.

It is clear, for instance, that a lack of awareness around PNH means that challenges for those living with PNH start already at diagnosis and persist throughout their whole disease experience. Improving awareness on all symptoms is key to making sure that the PNH patient journey is safer and that healthcare professionals are given the appropriate tools to support their patients. It is also essential that with increased awareness comes expedited access. The way to this, identified by the expert group, passes through the assessment of the clinical and economic benefit of PNH treatments. Here, it is essentials that HTA bodies also consider the indirect costs or non-health related benefits on new therapies, such as the ability to return to work.

Furthermore, experts have shown that a more holistic understanding of PNH, which can lead to considerable benefits for patients, is essential. This can only be done if appropriate measurement and collection of QoL data is put in place to understand the real impact of this ultra-rare disease. The frequency and severity of persistent symptoms, such as fatigue, which is so heterogenous and different from patient to patient, should be captured from a physical, psychological, functional, and social perspective with PNH specific patient report outcomes measurements.

Partnering4PNH has also brought to light existing best practices that, if made more widely available across geographies, could improve the patient experience. For instance, by further empowering patients and caregivers in the decision-making process, we can move towards a system of care that is patient centric. Specialist PNH nurses also play a crucial role in patient care and strengthening their role would bring significant value to patients and healthcare systems.

One thing is certain, as the outcomes and proposals of Partnering4PNH see daylight, there are many reasons to be optimistic. The time is right for the solutions proposed by the expert group to be implemented, as policy frameworks are changing around the world and in Europe, for instance, towards a new Orphan Medicinal Products Regulation and a new Health Data Space Regulation. The future brings considerable opportunities, and we are convinced that multistakeholder partnerships like Partnering4PNH should be the foundation for changes to come.

Annexes

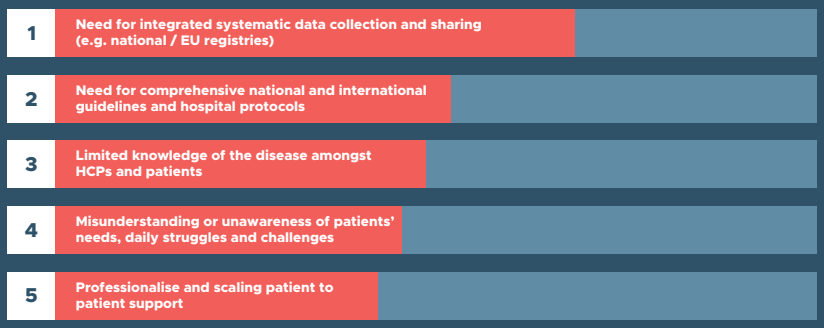
Annex 1: Brief Overview of Clinical Guidelines and Protocols for PNH Around The World

Country	Guideline name	Organisation / author	Year of most recent review	C5i recommendation	C3i recommendation
UK	PNH[62]	BMJ Best Practice	2012	Yes	No (although recently recommended by NICE)
Spain	Spanish consensus statement for diagnosis and treatment of PNH[63]	Sociedad Española de Hematología y Hemoterapia	2016	Yes	No
Germany	PNH[64]	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie	2022	Yes	Yes
France	Management of paroxysmal nocturnal haemoglobinuria[65]	HPN France Association	2020	Yes	No
Italy	Practical Guide for Patient with PNH[66]	Associazione Italiana Emoglobinuria Parossistica Notturna	2021	Yes	No
Norway	Norwegian guidelines for diagnosis and treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH)[67]	Tjonnfjord & Tjonnfjord (2013)	2013	Yes	No
Netherlands	Guideline Paroxysmal Nocturnal Haemoglobinuria[68]	Landelijke werkgroep PNH, Radboudumc Expertise Centrum PNH, and Stichting AA & PNH contactgroep	2016	Yes	No
Turkey	PESG PNH guideline[69]	PNH Education and Study Group	2016	Yes	No
Australia	Guidelines for the treatment of PNH through the lifesaving drugs program[70]	Australian Government Department of Health	2018 (since moved to PBS)[71]	Yes	No
Japan	PNH reference guide[72]	Akihiko Goto (2020)	2020	Yes	No
US	Therapies (webpage)[73]	Aplastic Anemia & MDS International Foundation	2022	Yes	No
Canada	How we treat paroxysmal nocturnal haemoglobinuria: A consensus statement of the Canadian PNH Network and review of the national registry[74]	Canadian PNH Network	2019	Yes	No
Brazil	Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria[75]	Cancado et al. (2020)	2021	Yes	No
Argentina	PNH: Argentinian Consensus on Diagnostics and Treatment[76]	Grupo Argentino de Interés en HPN	2013	Yes	No
Mexico	Mexican consensus on the treatment of paroxysmal nocturnal haemoglobinuria[77]	Góngora-Biachi et al. (2015)	2015	Yes	No

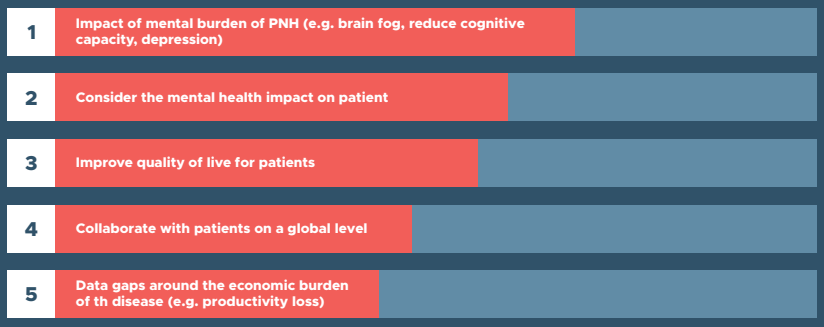
Annex 2: Snapshots From the Prioritization Exercise From Partnering4PNH

Prioritisation of Unmet Needs Exercise (slido.com)

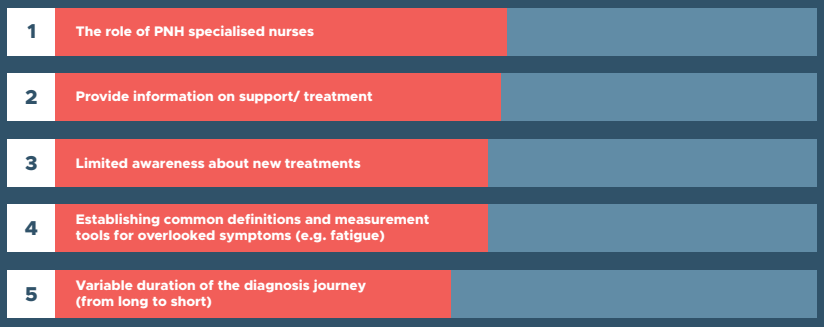
Awareness and education on PNH
Looking at the identified unmet needs on awareness and education on PNH, can you rank them in order of priority of action, from short-term to long-term?



Impact of PNH
Looking at the identified unmet needs for impact of PNH, can you rank them in order of priority of action, from short-term to long-term?



Diagnosis, care and treatment
Looking at the identified unmet needs for diagnosis, care and treatment, can you rank them in order of priority for action, from short-term to long-term?



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