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

Partnering
4 PNH
Aspire for change

Member Organisations of Partnering4PNH

AAMAC ACAAM
Aplastic Anemia & Myelodysplasia Association of Canada
Association canadienne de l'anémie aplasique et de la myélodysplasie

PNH CANADIAN ASSOCIATION OF PNH PATIENTS

HPN HEMATOLÓGICAS RARAS

The Royal Melbourne Hospital

PNH National Service
LEEDS & LONDON

PNH UKRAINE

Initiative sponsored by

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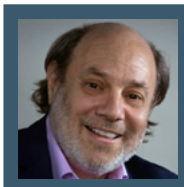


Barry Katsof
President and Founder, Canadian Association of PNH Patients, Canada

"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 Global Medical Affairs and Clinical Science Haematology, Swedish Orphan Biovitrum AB, Sweden

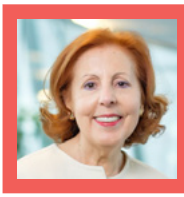
"It is really powerful when various stakeholders with different experiences but with common goals partner together to create a sustainable path for the rare disease community. This can lead to increased quality of life for patients, here represented by people living with PNH, and gains for society in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

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

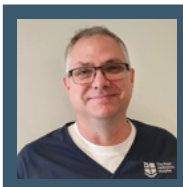
Jordi Cruz
President, Asociación de Hemoglobinuria Paroxística Nocturna, Spain

"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

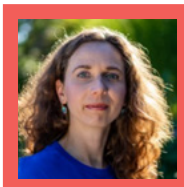


Maria da Graça Carvalho
Member of the European Parliament, European People's Party, Portugal



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"

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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.

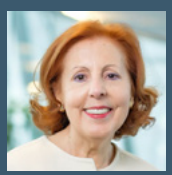
For example, a PNH diagnosis takes on average between 2 and 5 years which creates a profound negative financial and emotional impact on the patients and their families. To improve the long diagnostic journey, eliminate unequal access to treatments and offer a chance to a better quality of life for people 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)

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.