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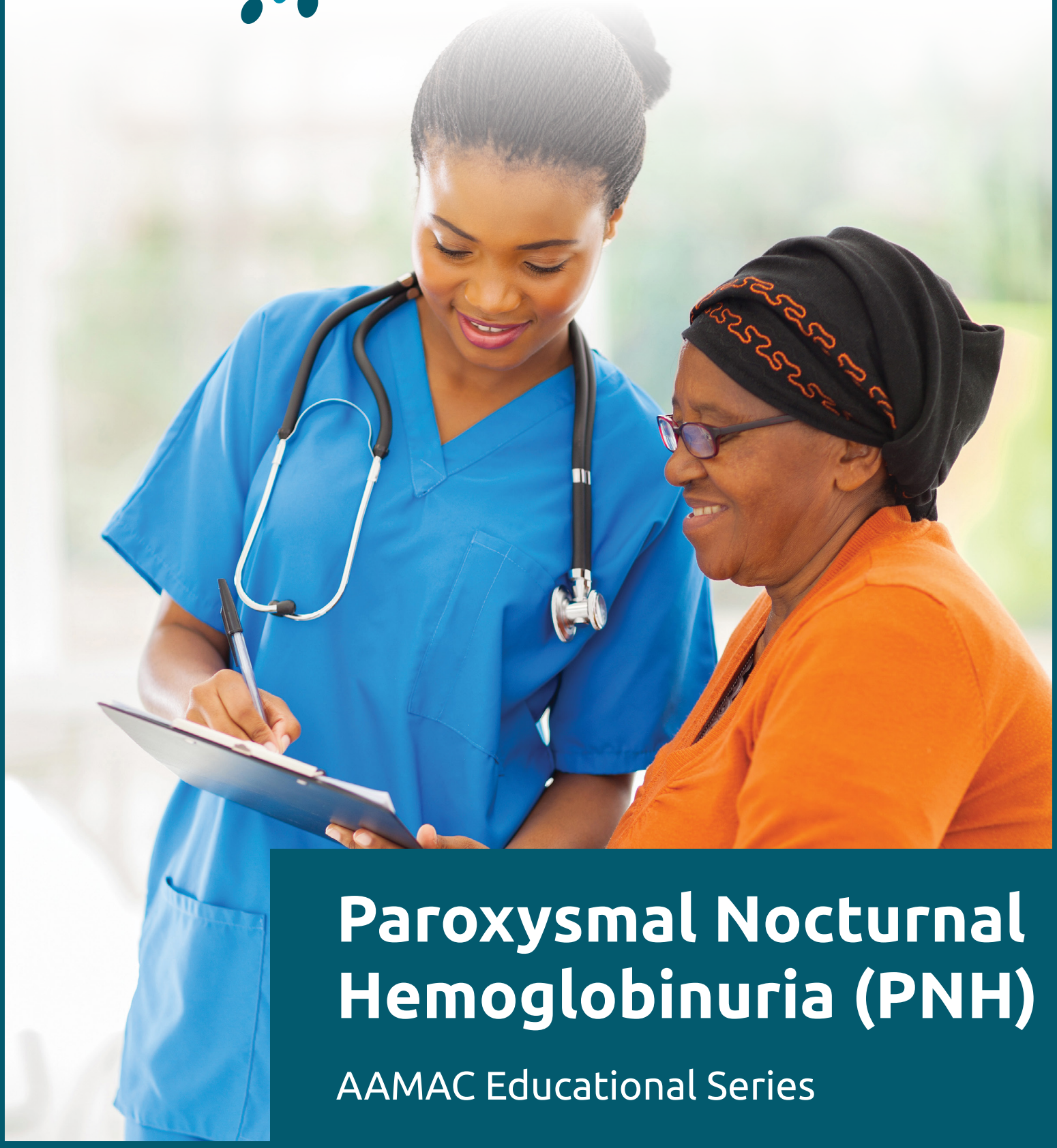
Aplastic Anemia & Myelodysplasia Association of Canada

Association canadienne de l'anémie aplasique et de la myélodysplasie



Paroxysmal Nocturnal Hemoglobinuria (PNH)

AAMAC Educational Series

The Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) is a federally incorporated and registered national not-for-profit charity guided by dedicated volunteer members of the Board of Directors and a distinguished team of medical advisors from across Canada. Our volunteer-run organization supports patients and caregivers across the country who are living with aplastic anemia (AA), myelodysplastic syndromes (MDS) and paroxysmal nocturnal hemoglobinuria (PNH). For more than 30 years, AAMAC has focused on education, advocacy, and research, and provides support for patients and care partners across Canada who are dealing with AA, MDS and PNH.

This educational booklet is a comprehensive resource for Canadians who are living with PNH and their loved ones, to support the journey of navigating this disease from diagnosis to treatment and beyond.

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1 | ABOUT THE DISEASE

About PNH

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare blood disorder where red blood cells are broken down prematurely. Physicians refer to this fragmentation of red blood cells as **hemolysis**. This occurs due to the absence of specific proteins on the surface of a person's blood cells, which normally shield them from the body's immune system.

There are three types of blood cells:

- **Red blood cells (RBCs)** are responsible for carrying oxygen from a person's lungs to cells throughout the body. Oxygen is carried on the hemoglobin (Hb) in the RBCs
- **White blood cells (WBCs)** defend the body against infection
- **Platelets** support the clotting of blood and help stop bleeding

With PNH, red blood cells break apart and release the hemoglobin contained within them. The discharge of hemoglobin is responsible for triggering many of the symptoms associated with PNH.

Bone marrow and blood cells

PNH is a *bone marrow failure disorder*, much like myelodysplastic syndromes (MDS) and aplastic anemia (AA). Bone marrow failure occurs when the marrow doesn't produce an adequate supply of blood cells - RBCs, WBCs, or platelets. Additionally, the blood cells that are manufactured may be defective or damaged. As a result, the body is unable to provide itself with the blood cells it requires to maintain essential functions.

The production of blood cells is referred to as **hematopoiesis**. These blood cells are manufactured within the bone marrow, which is a porous tissue found inside specific bones. Within the marrow, there are blood-forming stem cells that replicate to generate all three types of blood cells. Once these blood cells reach full maturity and become functional, they leave the bone marrow and go into the bloodstream. People in good health have enough stem cells to produce all the blood cells required by their bodies.

Every person with PNH experiences a certain level of bone marrow dysfunction, which can range from mild to severe resulting in diminished levels of RBCs, WBCs, and platelets. Depending on the level of bone marrow dysfunction, the symptoms of PNH may vary from non-existent to severe.

The name paroxysmal nocturnal hemoglobinuria comes from:

- Paroxysmal which means *irregular and sudden*
- Nocturnal which means *night*
- Hemoglobinuria refers to the presence of hemoglobin in urine, which darkens the urine's colour and can turn it red

Together, *paroxysmal nocturnal hemoglobinuria* refers to abrupt, sporadic occurrences of passing dark-coloured urine, particularly during the night or first thing in the morning. However, this description can be somewhat misleading, as many people diagnosed with PNH do not exhibit dark urine. It was also previously believed that hemolysis and the resulting hemoglobinuria only happened in sporadic episodes (paroxysms) and were more frequent during nighttime (nocturnal). However, it is now understood that although *hemoglobinuria* might seem to occur sporadically, *hemolysis* occurs continuously within the body throughout the day and night.

PIG-A gene mutation

PNH arises due to a genetic change, or mutation, in the **PIG-A gene**. Healthy RBCs possess a *protective layer of proteins* that shield them from potential attacks by the **complement system**, a group of proteins that circulate in the bloodstream and 'complement' the work of WBCs by combatting infections. The *gene responsible for producing this protective shield* is known as PIG-A.

Listed below are the steps leading up to PNH:[1]

- The mutated stem cell replicates or makes 'clones' of itself, resulting in a large number of bone marrow stem cells with the PIG-A mutation
- These abnormal cells develop into blood cells (RBCs, WBCs and platelets) bearing the mutated PIG-A gene, referred to as PNH blood cells or **PNH clones**
- PNH RBCs do not have the protective protein shield present in normal RBCs, rendering them vulnerable to attack and destruction of the **complement system**

Many people in good health possess a limited quantity of PNH stem cells. However, for people with PNH, these stem cells multiply rapidly, resulting in an abundant production of mature PNH clones. Patients with PNH may have weakened bone marrow caused by conditions like AA, MDS or another underlying, possibly undetected, bone marrow disorder.[1]

Types of PNH

Type of PNH	Treatment Approach*
Classical PNH **-** Approximately one-third of people with PNH clones in their bodies exhibit a *classic* manifestation of the PNH disease marked by evident *hemolysis*, its related symptoms, and a notable existence and impact of blood clots which are typically associated with PNH.[2]	These patients receive maximum benefit from starting treatment with *complement inhibitors*[2] as soon as possible following diagnosis.
Subclinical PNH **-** Patients with what is referred to as *subclinical* PNH have a very small number of PNH clones and do not typically show evidence of hemolysis or blood clots in laboratory tests.[3] Subclinical PNH does not cause symptoms that impact the health of the patient.	These patients usually do not need to be treated for PNH unless they show notable symptoms[4], and should be monitored for any change in status.
Bone Marrow Failure (BMF) and PNH **-** People with PNH clones who are living with a bone marrow failure disease, like AA or MDS, might show a few PNH-related symptoms, the severity of which are closely related to their number of PNH clones. Most of these patients have a very small number of clones with few symptoms and have the subclinical form of PNH.[2]	In these patients, treatment should primarily focus on their bone marrow failure disorders, such as AA and MDS.[5]

*Detailed information on treatment is provided later in this booklet

Incidence and prevalence of PNH

PNH is a very rare disease which is thought to impact males and females at roughly the same rates, although certain studies suggest a slightly higher incidence in females. Its estimated prevalence ranges from 0.5 to 1.5 cases per million in the general population. The condition has been observed in people from diverse ethnic backgrounds and detected in various parts of the world. It may occur more frequently in people from Southeast or East Asia, where AA is also more prevalent. While PNH can affect people of any age, the typical age of diagnosis is 30.[6] It can also be diagnosed in children.[7,8]

The only recognized risk factor associated with the development of PNH is being diagnosed with AA. About 50% of patients living with acquired AA develop PNH clones[9] and more than 10 out of every 100 patients with AA will eventually develop PNH that requires treatment.[1,10] Conversely, some people with PNH may also develop AA. Common symptoms like low blood cell counts can be shared between PNH and AA patients. Also of note, about two out of every 100 patients with PNH will subsequently develop MDS another bone marrow disorder.[1]

2 | SIGNS & SYMPTOMS

Hemolysis

Chronic hemolysis is at the core of all symptoms and physical observations related to PNH. It heightens the risk of blood clot formation and some people may develop both chronic and acute kidney conditions as a result.

Symptoms of *mild hemolysis* may include:

- Fatigue
- Rapid heartbeat
- Chest pain
- Headaches
- Breathlessness while exercising

In cases of *severe hemolysis*, additional symptoms may manifest, including:

- Intense fatigue
- Swallowing challenges (*dysphagia*)
- Sudden painful spasms impacting the stomach and the esophagus (*esophageal spasms*)
- Erectile dysfunction and impotence
- Crampy abdominal pain

Blood clots[6]

Up to 45% of PNH patients experience **blood clots**[11], particularly in their veins, a condition known as **venous thrombosis**. There is a complex interplay between the *complement* and *coagulation* system - that supports the clotting of the blood - which increases the risk of thrombosis. Blood clots can travel through the bloodstream to various parts of the body, potentially leading to life-threatening complications. Organs like the stomach, liver, and brain may suffer reduced or blocked blood flow as a result.

The specific symptoms linked to *venous thrombosis* vary based on the body part affected.

- Blood clots that occur in the **lungs** may result in chest pain, shortness of breath, dizziness, coughing up blood or palpitations
- Blood clots that occur in the **legs** may present with leg swelling, tenderness, pain or redness. The deep veins present in the lower limbs are the most common areas of blood clot formation[12]
- When blood clots impact the **liver**, they can lead to symptoms like jaundice and abdominal pain, or potentially trigger a condition called **Budd-Chiari syndrome**, a condition where the veins that drain the liver, called the hepatic veins, are blocked or narrowed by a clot[13]
- Blood clots that affect the **bowels and stomach** may cause sharp abdominal pain or a sensation of bloating or fullness
- Blood clots impacting veins in the **brain** might lead to symptoms such as headaches or cognitive difficulties
- More rarely, blood clots might develop in the **arteries**, posing life-threatening risks by obstructing blood flow to critical organs like the heart

The ongoing hemolysis associated with PNH is a key driver of blood clot formation. However, there are also several other reasons for the formation of blood clots in people with PNH, some of which are well-studied and fairly well-understood, while others are still under investigation.

Anemia

When there is a reduced number of circulating RBCs, it results in a condition called **anemia**. Similarly, a decreased overall count of WBCs is referred to as **leukopenia**, and a diminished level of platelets is known as **thrombocytopenia**. In some patients with PNH and more prominent bone marrow failure, or those with MDS or AA, the cytopenias (low blood counts) can be so severe that they require regular transfusions of red blood cells and, more rarely, platelets. There is no replacement blood product for low WBCs. People who have *anemia* may encounter symptoms such as:

- Varying degrees of tiredness
- Difficulty concentrating or staying alert
- Loss of weight and/or appetite
- Developing pale skin
- Difficulty breathing
- Rapid heartbeat or heart palpitations
- Dizziness and/or fainting
- Trouble climbing stairs or exercising

People with **leukopenia** face a heightened vulnerability to infections, especially fungal and bacterial and experience symptoms such as:

- Repeated infections and fevers with a higher risk of becoming more ill with infections
- Bladder infections leading to pain urinating or urinating more often
- Pain or a bad odour when urinating
- Lung infections leading to breathing difficulties and coughing
- Severe coughing
- Shortness of breath
- Mouth sores
- Stuffy nose and sinus infections
- Skin infections, redness or swelling
- Sore throat
- Patches in the mouth that are red or white
- Diarrhea
- Vaginal itching or unusual vaginal discharge

People with **thrombocytopenia** are at an increased risk of experiencing excessive bruising even from minor injuries, as well as sudden bleeding from mucous membranes, particularly in the gums and nasal passages. They may experience:

- Bruising
- Heavier menstrual periods than normal
- Nose bleeds
- Flat and small red spots under their skin (called petechiae) due to bleeding
- Bleeding gums after brushing their teeth and following dental work
- Hemorrhoids

It is important to know that people living with PNH may not exhibit all the symptoms usually associated with this disease. Those affected should speak with their PNH specialists and healthcare team about their particular case, accompanying symptoms, and overall **prognosis** – the likely development of the disease.

Other medical concerns

Some of the symptoms of PNH *may* lead to life-threatening issues. For example, in some cases, the development of **blood clots** can be fatal or lead to severe complications. Other complications, like **pulmonary hypertension**, make patients vulnerable to heart failure. When PNH impacts **kidney function**, patients can be more vulnerable to kidney failure.

A serious issue faced by people with PNH is the **risks associated with pregnancy** for both the mother and the unborn child. Expectant mothers with PNH could potentially experience complications like preeclampsia (a serious condition that raises blood pressure), blood clots, stillbirth or premature birth, low birth weight, and the need for a cesarean section. Any surgery could be risky for people with PNH since they are more vulnerable to blood clots. However, recent research shows that while PNH in expectant mothers could potentially lead to a higher likelihood of pregnancy-related issues, treatments for PNH have been shown to be effective in managing PNH during pregnancy for both the mother and child.[14]

3 | IMPACT OF PNH ON QUALITY OF LIFE

A diagnosis of PNH can be very difficult for the patient and their loved ones, bringing with it a negative impact on quality of life.[15,16,17] Some patients experience an abrupt and swift onset of life-threatening symptoms that progress rapidly. In contrast, other patients face a long-term course of chronic illness with minimal life-threatening complications.[18] However, the overall impact of PNH potentially leads to significant emotional challenges, like the fear of death and survival, feelings of isolation, self-consciousness and difficulty coming to terms with the diagnosis and its impact on one's life. A study conducted in 2019 also showed **severe fatigue** and a **decreased quality of life** in people living with PNH.[19] The fatigue may make it difficult for a person living with PNH to manage their work schedule and they may need to cut back hours. Their daily routine may be further interrupted by the need for periodic drug infusions. Other studies have also reported that people with PNH who depended on blood transfusions had notably low scores in quality of life, compared to those who were not dependent.[19,20]

Living with PNH can lead to feelings of anxiety, stress, and profound fatigue, which can, in turn, present **challenges in maintaining relationships with family and friends**. In addition, PNH may become a reason for **sexual problems** since it may lead to erectile dysfunction and a feeling of extreme tiredness in both men and women. In these situations, being open and honest with loved ones about these feelings and issues will make it easier for them to provide help and support.

4 | DIAGNOSING PNH

A diagnosis of PNH is typically confirmed through a specialized blood test known as **flow cytometry**. However, as part of the diagnostic procedure to rule out PNH-related complications and gauge its severity, several other assessments are conducted. These assessments may include other blood tests, a bone marrow biopsy, imaging studies such as x-rays and CT scans, ultrasound examinations, and additional laboratory analyses, including urine tests.

Tests to diagnose and monitor PNH

In the diagnosis and regular monitoring of PNH, several laboratory tests are commonly performed by physicians. These include *lactate dehydrogenase (LDH)*, a *complete blood count (CBC)*, a *bilirubin test*, *creatinine*, a *reticulocyte count* and *flow cytometry*, in addition to other blood and urine tests and bone marrow tests. Combined with observable symptoms, these tests provide a comprehensive understanding of the condition of PNH and support its effective management. Out of these, flow cytometry constitutes the primary diagnostic test for PNH.

Flow cytometry - This is a blood test that entails suspending blood cells within a fluid stream and guiding them past an electronic detection device. This examination can assess both the white and red blood cells, to determine the PNH 'clone' size. Clone size denotes the proportion of red and white blood cells in the body that are impacted by PNH and missing critical protective surface proteins. A larger clone size indicates a higher presence of PNH cells. However, even people with a clone size as low as 10% may experience symptoms that can significantly impede their daily lives.

Lactate dehydrogenase (LDH) - An enzyme found in red blood cells (RBCs), LDH serves as an indicator of the extent of hemolysis in the body. Monitoring LDH levels offers valuable insights since LDH levels are high in patients experiencing significant hemolysis. Regular LDH testing plays a crucial role in monitoring and managing this condition and establishing a baseline LDH level is essential for tracking one's response to treatment over time.

Complete blood count (CBC) - The CBC is a comprehensive test that examines various components of the blood, including RBCs, WBCs, and platelets and supports monitoring of the disease. Its purpose is to identify issues with the bone marrow that can be the cause of low levels of various blood components and help to assess the degree of blood cell breakdown.

Bilirubin test – This test measures the overall concentration of bilirubin in the bloodstream. Elevated levels of unconjugated or indirect bilirubin suggests the breakdown of RBCs.

Reticulocyte count – This test is used to gauge the quantity of young RBCs present in the bloodstream. When mature RBCs are broken down by PNH, the bone marrow responds by releasing reticulocytes (young RBCs) from the bone marrow into the bloodstream. Reticulocytes may be inappropriately normal or low in PNH patients with more prominent bone marrow failure.

Bone marrow assessments – An analysis of the bone marrow is also used for diagnosing PNH. Initially, a physician extracts a sample of bone marrow aspirate using a hollow needle usually from either the pelvic or breastbone. In addition, a solid segment of bone marrow is obtained as part of a bone marrow biopsy. This procedure may cause temporary pain when the freezing needle is inserted, but the discomfort is brief and should not persist.

The physician will examine the liquid bone marrow using a microscope and forward the specimen of bone marrow to a laboratory for further analysis.

Bone marrow tests support:

- Confirmation of a PNH diagnosis
- Building an understanding of how poorly or effectively the bone marrow is building blood cells

In addition, they show:

- The cellularity (number of cells within a tissue sample) of the bone marrow
- The specific types and quantities of cells being produced by the bone marrow
- Levels of iron in the bone marrow
- Abnormalities in the chromosomal (DNA) makeup

5 | COMORBIDITIES OF PNH

It is important to note that as with any disease, other **comorbid** conditions can exist in people living with PNH. It is important to speak to your physician about how to diagnose and manage them.

6 | LIVING WITH PNH

Navigating Care

Preparing for Appointments: It is simple to overlook important questions during an in-person or virtual visit with your PNH specialist. Before an upcoming appointment, it is important to jot down questions and discuss these thoroughly with the hematologist/oncologist or their support team. It is also helpful to carry a notepad for writing down the responses or, if allowed, record the session to review later. If possible, bring a trusted companion to the appointment to help ensure that all questions are answered.

Managing Medical Information: It is a good practice to keep your health information, including lab results and medical records, in a single location. Consider organizing and storing these documents in a notebook, on your computer, or in an online tool using a smartphone or tablet app to easily access and refer to them whenever needed. Ask your doctor if it is possible to gain access to your results through the hospital's electronic medical record (EMR).

The Treatment Plan: It is important to collaborate with your physician in developing a treatment plan. This plan should consider the diagnosis, the current treatment options available, and the ultimate goal of treatment. Each person's treatment plan will be unique and tailored to factors such as age, blood count measurements, overall well-being, and other considerations. It is important to thoroughly review the treatment plan provided and ensure that you are comfortable with the approach. A well-crafted treatment plan should empower you, fostering a sense of control and optimism for the future.

Using Support Systems: Coping with PNH and navigating the treatment process can be challenging. There may be moments of fatigue, illness, or anxiety in this situation. This is why it is important to seek assistance. Consider whether family members or friends can help with tasks such as grocery shopping or providing transportation to and from medical appointments. You might be pleasantly surprised by the willingness of your loved ones to lend a helping hand when asked.

Consider scheduling a session with a counsellor or mental health professional. If possible, seek out someone who has a background in assisting people facing health challenges like PNH. Ask your physician about the availability of support networks for people coping with PNH. Becoming a part of a support group can offer valuable opportunities to exchange experiences and receive advice on effectively managing life with PNH or similar conditions. Interacting with people who genuinely comprehend your situation can have a significant impact on your overall quality of life.

*For more **information on PNH support groups in Canada**, please contact the Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) at info@aamac.ca or 1-888-840-0039.*

Coping with Stress: Coping with a serious illness can lead to feelings of being overwhelmed, stressed or down. People often find themselves discontinuing activities they once enjoyed and withdrawing from social interactions. While medications and various treatments can alleviate symptoms and improve blood counts, they may not effectively address emotional well-being. Therefore, exploring mind-body therapies, which centre on reducing stress and enhancing emotional well-being is strongly recommended. These therapeutic approaches can also provide relief from pain and enhance vitality. Consider whether treatments or practices such as meditation, deep breathing exercises, aromatherapy, yoga, tai chi, acupuncture, or massage therapy may be worth a try.

Doing other simple things that you love, which make you smile, could also be very meaningful. This could include taking up hobbies, enjoying nature, or other activities that may offer a welcome distraction.

***IMPORTANT:** Before exploring mind-body therapies, consult with the PNH specialist who oversees your treatment to discuss any potential risks of bleeding or infection. Your healthcare facility may have dedicated professionals who can assist you in devising a plan tailored to your unique needs.*

Dealing with Fatigue: Coping with PNH can pose challenges in managing energy levels, with persistent fatigue often taking a toll. Fatigue is characterized by profound exhaustion and the depletion of our body's systems, leading to drowsiness, weariness, and physical, cognitive, and emotional weakness. Its effects are felt in many aspects of daily life, impacting mood, confidence, and emotional stability, and cannot be improved solely with rest. To effectively address this, identify activities that drain your energy and those that rejuvenate you, such as spending time with a close friend or taking a revitalizing walk. Energy conservation revolves around striking the right balance in this regard.

1. **Prioritize and schedule your time -** Evaluate your tasks and identify your top priorities. Avoid overloading your schedule, especially if it affects your concentration or memory. Use lists for shopping and maintain diaries or notepads for appointments
2. **Regulate your pace and positioning -** Plan regular rest breaks throughout the day. Acknowledge your accomplishments, seek assistance when needed, and don't hesitate to decline additional commitments. Organize your environment to minimize unnecessary bending or reaching
3. **Use relaxation techniques -** Incorporate practices like visualization, breathing exercises, or meditation into your daily routine. These practices can help you feel more in charge of your situation.
4. **Address mental fatigue -** Understand that fatigue doesn't impact solely your physical well-being; it can also trigger feelings of anxiety, stress, and overwhelm. If comfortable, share your feelings with those around you to seek support and understanding.

Surgery and PNH: Surgery is considered risky for people living with PNH because it:

- Causes the *complement system* to become more active, which may lead to *hemolysis*
- Elevates the risk of blood clots
- May lead to bleeding in people who have a low count of platelets
- Could necessitate platelet or red blood cell transfusion ahead of surgery or the use of blood thinners to prevent blood clots

If you need to go ahead with surgery, it is important to:

- Ensure that the physician treating your PNH has a discussion with the surgeon
- Make sure that you are given a blood thinner after surgery if the platelet count allows and the physician advises it

Nutrition and Exercise: It is crucial to maintain proper nutrition and dietary habits, in addition to following your PNH treatment plan. Ideally, your healthcare provider can assist you in devising an optimal nutrition plan. For people living with PHN, it is advisable to follow a wholesome and balanced diet that is rich in fruits and vegetables. However, there are no dietary restrictions in patients living with PNH. To ensure your body receives adequate folic acid and iron, your physician may recommend an over-the-counter supplement. Folic acid and iron play a notable role in the production of red blood cells. However, some patients with PNH who require regular transfusions can become iron-overloaded and thus it is important to ensure your supplements are reviewed at each appointment.

IMPORTANT: *Always consult with your healthcare provider to determine the most suitable supplements for your needs, and seek their guidance before taking any medications, vitamins, or herbal supplements.*

Physical exercise can also improve your overall well-being while managing PNH. While you might have faced certain physical limitations in the past, receiving treatment may enable you to reintegrate simple activities such as walking or light household chores, and even expand your physical capabilities. However, some of the symptoms you experienced before treatment may persist, so it is advisable to begin any new exercise routine only when you are in optimum health and with the approval of your physician.

Financial Planning: People living with diseases like PNH frequently describe a negative impact on their financial circumstances while undergoing treatment. Monthly expenses can escalate and might be due to an increase in travel expenses, childcare, and the need to take time off work for medical appointments. The household income could diminish if you or your caregiver need to stop work or reduce hours, either on a permanent or temporary basis, due to the diagnosis. To help reduce stress and worry, consider following the steps below:

- Start by **evaluating your income and financial assets**. Questions to ask include:
    - What kind of paid or unpaid medical leave is available to you and/or your caregiver?
    - Can either you or your partner consider part-time employment?
    - Do you have any Income Protection or any critical illness insurance, or is it integrated into a life insurance policy?
    - Do you have access to existing funds or a line of credit, if needed?
- Next, **make a list of any expenses that must be addressed in the near term**. If you don't already have one, create a budget that reflects the realities of managing finances while undergoing treatment.
- You may wish to check if **getting life insurance** is possible at this stage, if you didn't have it before your diagnosis
- If you are **incapable of meeting your usual mortgage or loan obligations due to severe health issues**, it is recommended that you promptly inform the appropriate institutions. Banks and similar financial entities usually offer specific accommodations for customers facing financial distress due to health-related challenges

*For **information regarding financial assistance available to Canadians dealing with PNH**, feel free to reach out to the Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) at info@aamac.ca or 1-888-840-0039.*

Discussion with your Employer: It is your choice as to whether or not to inform your employer that you have been diagnosed with PNH. Regardless, it is important to be aware of the criteria for short and long-term disability leave and other private health care coverage you may have through your employer.

While the majority of employers support employees dealing with an illness equitably and within the bounds of the law, certain employers may impose unwarranted and occasionally unlawful obstacles on their staff in such situations.

Concerns may arise regarding potential termination, lack of employment, reduced job status, rejection of advancement, denial of benefits, unwelcome reassignment, or unjust treatment by colleagues.

IMPORTANT: *Depending on your specific circumstances, it may be advisable to consult with an expert in employment law who is knowledgeable about employment rights for people coping with serious illness.*

Advocating for Yourself: At any point in your journey with PNH, you could face a situation where you may need to advocate for yourself or your loved one. These opportunities may require you to communicate with decision-makers at various levels including your physician, your local hospital where you or your loved one is treated, or the government to gain access to care and treatment.

A first step to addressing any roadblocks along the way may be discussing your situation with a support group where others may have lived through a similar experience and could potentially help you with useful advice. For assistance in navigating situations requiring advocacy for yourself or your loved one, you may also wish to contact the *Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)*.

7 | TREATMENT

There are numerous treatment options for people dealing with PNH, depending upon the severity and progress of the condition.

The mainstay of treatment for PNH is complement inhibition. The only potential cure for PNH is a **bone marrow transplant**. Some treatments primarily provide supportive care, whereas targeted therapies can deliver substantial advantages by addressing the symptoms of the disease.

Without treatment, roughly 33% of PNH patients will not exceed a five-year survival rate.[21] Fortunately, there are Health Canada-approved PNH treatment options that have demonstrated effectiveness in restoring a patient's life expectancy to that of a person in good health. Current clinical care in Canada recommends beginning therapy, particularly complement inhibitors, as soon as possible following diagnosis.

Outlined in this section are the various therapies that are currently used in Canada in the management of PNH. Although it is important to know many treatments are still being studied or in development and may become available in the future.

Supportive Therapy

Folic Acid (Folate) and iron: Certain PNH patients are provided with folic acid supplements to increase folate levels. When the bone marrow tries to counterbalance the hemolytic anemia caused by PNH by increasing the production of red blood cells (RBCs) in the bone marrow, the demand for folate is elevated. In cases of iron deficiency, often stemming from red blood cell breakdown and the subsequent excretion of iron through urine, supplementary iron becomes necessary.

Anticoagulation: PNH specialists may use anticoagulation therapies, which are medications aimed at preventing the development of blood clots by thinning the blood. Anticoagulation is required in all patients who have experienced a blood clot as a result of PNH. The duration of therapy may vary from 3-6 months to indefinitely, depending on the circumstances of the blood clot. Some patients may be started on anticoagulation even if they haven't had a blood clot, for prevention during situations which are high risk for blood clots. For example, during pregnancy, surgeries or when there is active hemolysis and a delay in starting other PNH treatments.

Patients with PNH and low platelets who require anticoagulation must be monitored closely as there is a higher risk of bleeding. Some oral anticoagulants available in Canada include apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Lixiana®), rivaroxaban (Xarelto®), and warfarin (Coumadin©) among others.[22] There are also intravenous (IV) and subcutaneous (SC) blood thinners.

Some of the side effects of anticoagulation include the possibility of an increased risk of bleeding, bruising and unexpected drug interactions.

Blood Transfusions: People with PNH who have low blood cell counts may require blood transfusions. This involves the administration of RBC transfusions to address anemia and platelet transfusions to manage or prevent severe bleeding. During a blood transfusion, components of donated blood are introduced into the circulatory system intravenously to help boost diminished blood counts. Patients who are potential candidates for a bone marrow transplant should attempt to limit blood transfusions where possible, to prevent the formation of antibodies which can make finding a match for the transplant more difficult.

Regular blood transfusions increase the risk of iron overload, allergic symptoms, and complications which can affect the heart and lungs or lead to transfusion-related complications.

Iron Chelation Therapy: People with PNH who undergo frequent blood transfusions may experience iron accumulation in their bodies. This is evaluated through periodic blood tests, such as serum transferrin saturation test, and ferritin, to measure the amount of iron in the blood, conducted multiple times annually. If recommended by a physician, there are several iron chelation therapies (oral, subcutaneous, or intravenous) approved in Canada that have been proven to address iron overload in patients with PNH and other bone marrow disorders, including deferasirox (Exjade®, Jadenu®), and deferoxamine (Desferal®).

Iron chelation therapy can potentially lead to an increased risk of impaired colour vision and hearing loss. Patients taking these treatments should undergo periodic vision assessments conducted by an ophthalmologist and hearing evaluations conducted by an audiologist.

Treatments for PNH

Bone Marrow Transplantation: Bone marrow transplantation remains the sole treatment capable of providing the potential for complete recovery from PNH. In this procedure, healthy stem cells from a donor completely substitute all the patient's bone marrow stem cells. Due to the associated risks of health complications and mortality, this treatment option is typically reserved for patients who have concurrent bone marrow failure (AA or MDS). In patients with classical PNH, bone marrow transplants are not performed as a treatment, as complement inhibitors are usually effective and well tolerated. The most common method of bone marrow transplantation employed in PNH treatment is **allogeneic bone marrow transplant**.

In the process of an allogeneic bone marrow transplant, the affected individual's bone marrow is typically eliminated using chemotherapy, immunotherapy, radiation, or a combination of these treatments. Subsequently, healthy marrow from a donor is introduced intravenously into the body. This donor marrow migrates to the bone marrow site and eventually starts the production of new blood cells. The most compatible donor, or 'match', for a bone marrow transplant is typically a sibling who is a blood relative. However, in certain cases, people may need to undergo a search for an unrelated, matched donor. Bone marrow transplantation has the potential to cure the underlying bone marrow dysfunction and eliminate the defective PNH stem cells.

Due to the risk of bone marrow transplantation, there is an extensive assessment of the patient and the disease severity to determine if someone is eligible for bone marrow transplants. It is important to understand the potential for complications, occurrences of treatment ineffectiveness, and even the risk of death.

Drug Therapy: In recent years, there has been considerable innovation in the development of PNH drug therapies. Currently approved treatments, including **eculizumab**, **ravulizumab** and **pegcetacoplan**, can efficiently prevent the immune system from attacking and breaking down the red blood cells prematurely. Overall, these drugs have shown positive results in decreasing hemolysis and improving anemia and, in some patients, considerably decreasing or even removing the need for blood transfusions. Additional benefits include significantly decreasing the risk of blood clots, increasing energy levels, and potentially even restoring people's life expectancy to what is considered normal. Patients taking eculizumab, ravulizumab and pegcetacoplan have also shown improvements in renal function over time.

Both eculizumab and ravulizumab bind to the C5 complement protein, a component of the body's **complement system**, and obstruct it, inhibiting its impact on red blood cells. The result is a decrease in the destruction of RBCs while alleviating symptoms and mitigating the disease's impact. Pegcetacoplan, on the other hand, binds to the immune system protein known as complement protein C3. These drugs are known as **complement inhibitors**. They have become the mainstay of treatment for all PNH patients who are experiencing symptoms.

Eculizumab is approved in Canada to treat patients with PNH who are 11 years and older[23] and is given by intravenous infusion once every two weeks by a healthcare professional. *Ravulizumab* is approved to treat PNH patients over one month of age[24] and is administered by a healthcare professional through intravenous infusion once every 8 weeks.[25] *Pegcetacoplan* is approved for the treatment of adults with PNH who are unable to tolerate or do not adequately respond to C5 inhibitors (eculizumab, ravulizumab). Pegcetacoplan is self-administered through a **subcutaneous** (under the skin) **biweekly infusion**.

Some common side effects of eculizumab and ravulizumab include headache, infections of the respiratory tract, nausea and/or vomiting, fever, and high blood pressure among others. A few common side effects experienced by patients taking pegcetacoplan include reactions at the injection site, abdominal pain, tiredness, pain in joints and limbs, dizziness, and headaches, among others.

Before starting these treatments, it is also important to discuss if you are **pregnant** or planning to start a family to talk about any potential risks. The same applies to **breastfeeding** mothers.

Complement inhibitors do not treat the PNH clone, but rather the complement symptom that is responsible for the blood cell breakdown and the majority of the symptoms of PNH. Thus, complement inhibitors are continued indefinitely once started.

Vaccination on Complement inhibitors: Eculizumab, ravulizumab and pegcetacoplan may impact the body's ability to combat certain infections. Before receiving any of these treatments, patients must get **vaccinated** for *meningococcal infections* that can occur in the blood. Pegcetacoplan might also increase one's risk of developing infections due to other kinds of bacteria such as *Neisseria meningitidis, Haemophilus influenzae type B* and *Streptococcus pneumoniae*. If you have received these vaccinations in the past, speak to your physician for guidance on whether an additional vaccination is necessary.[18,26,27]. Some PNH physicians may also recommend that you stay on a preventative antibiotic for the duration that you are on a complement inhibitor.

It is critical to keep your vaccination record up to date as infections can trigger your PNH to become more active. Seasonal flu vaccines are designed to protect against the specific influenza viruses that research suggests will be prevalent during the cold season. Patients with PNH should be encouraged to receive COVID-19 vaccines, even if they have previously had a COVID-19 infection.[28] Remember to inquire whether your family members and those near you should consider getting the flu or COVID-19 vaccine as well. This precautionary measure can potentially lower the risk of contracting these viruses.

Extravascular Hemolysis (EVH) - Despite the effectiveness of these medications in improving the well-being and survival of PNH patients, a small percentage of PNH patients treated with C5 inhibitors may still encounter persistent anemia. Multiple factors may contribute to this, such as bone marrow failure or deficiencies in vitamins (folate) or hormones (erythropoietin). In certain cases, ongoing anemia may be attributed to extravascular hemolysis (EVH) in patients who are on a C5 inhibitor (eculizumab or ravulizumab).[29] EVH occurs when red blood cells are tagged for destruction by C3 and destroyed in the liver or spleen.[30] EVH may lead to symptoms associated with anemia, like fatigue. In cases where a patient experiences EVH, their PNH specialist may recommend another therapeutic approach such as pegcetacoplan which manages both intravascular and extravascular hemolysis.

Note: *Before beginning a new therapy, it is advised that patients review the product monograph and discuss with their physician the pros and cons of taking the medication. The product monograph will include possible side effects, risk factors and other information to consider when beginning a new medication.*

Clinical Trials

Clinical trial research studies involve human participants to evaluate the safety and impact of a specific treatment. Results from clinical trials could be used for the approval of treatments for Canadians or to compare against established approaches to treating a disease. Visit the Government of Canada website to learn about clinical trials in greater detail.

Visit the AAMAC clinical trials page for updates on the latest clinical trials for PNH and speak with your PNH specialist about any clinical trials that you may be eligible for. It is an exciting time for PNH patients and physicians with a number of new treatments in development which aim to target the complement system in different ways.

8 | DISEASE MANAGEMENT

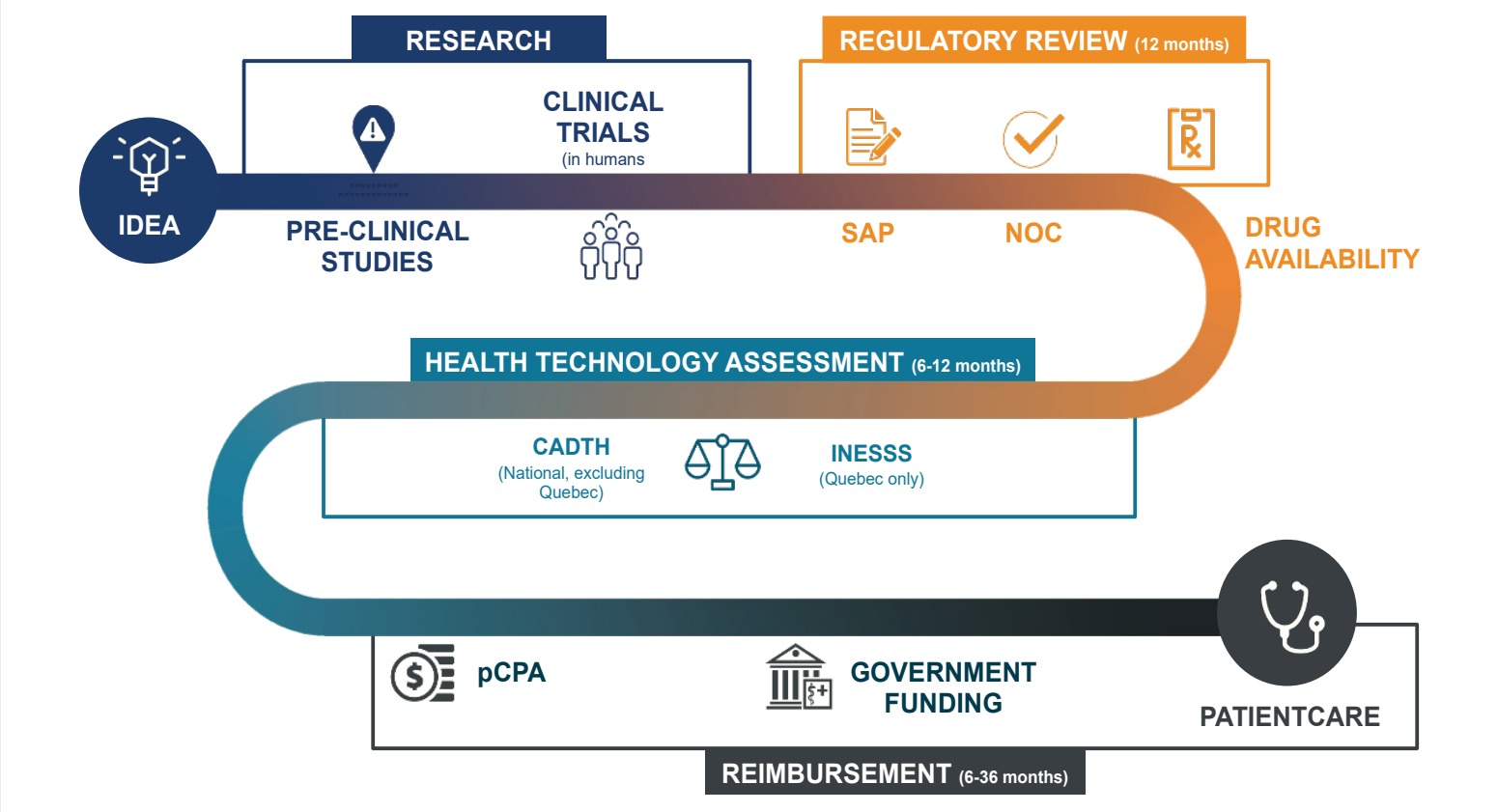
In order to take ownership of managing your PNH by tracking your symptoms and progress with treatments, try using the following resources from the **Aplastic Anemia and Myelodysplastic Association of Canada (AAMAC)** and the **Aplastic Anemia and MDS International Foundation (AAMDSIF)**:

1. Patient Tracker
2. Appointment Tracker
3. Blood Transfusion Record
4. Symptom Tracker
5. Platelet Transfusion Record
6. My Health Care Team
7. Emergency Room Card

Living with a disease like PNH brings various challenges, and you will have good days and not-so-good days. As you go through your journey with PNH, you will find that knowledge combined with the right support from health care experts, family and friends will make all the difference to your well-being and quality of life.

9 | ACCESS TO TREATMENTS IN CANADA

Processes Involved in the Approval and Public Funding of Treatments in Canada



Source: EVERSANA

Regulatory Review

For a medication to be available to Canadians, Health Canada (a department of the Government of Canada) must first approve it for safety, efficacy and quality. As part of the regulatory review process, Health Canada examines various scientific data, including clinical trial studies, to assess the potential benefits and risks of the medication. Once approved, the treatment will be issued a **Drug Identification Number (DIN)** and a **Notice of Compliance (NOC)**. The NOC then allows a pharmaceutical company to market and sell that drug in Canada, as well as qualified healthcare professionals to prescribe the treatment.

For more information, visit the Health Canada Drug and Health Products page.

Special Access Program

In cases of severe or life-threatening illnesses, when conventional treatments have proven ineffective, are unsuitable, unavailable, or offer limited choices, a physician may make an application on behalf of a patient **for a medication that has not yet been approved by Health Canada**. Application is made to the Special Access Program (SAP) within Health Canada's Therapeutic Products Program.

If approved, the SAP then authorizes the release of the drug to the physician, who in turn administers it to the patient. While a successful SAP application allows a non-approved medication to be brought into the country, it does not address who is required to pay for treatment.

For more information, visit the Health Canada Special Access Programs: Overview page.

Health Technology Assessment (HTA)

Health Technology Assessment (HTA) is the process whereby a health technology or treatment is assessed to determine the value of that technology and how it should be used in a health system. In Canada, we have two HTA bodies – the Canadian Agency for Drugs and Technologies in Health (CADTH) and the *Institut national d'excellence en santé et en services sociaux (INESSS)*.

CADTH

CADTH is the national agency (excluding Quebec) that makes recommendations to the public drug plans in Canada as to whether or not a particular medication should be publicly funded. They do so through what is called a Reimbursement Review, which is a comprehensive assessment of the clinical effectiveness and cost-effectiveness, as well as patient and clinician perspectives, of a treatment. While these reviews are non-binding on the public drug plans, they do help to guide the ultimate reimbursement decisions of the federal, provincial, and territorial governments.

For more information, visit the CADTH website.

INESSS

INESSS is the provincial agency in Quebec that makes recommendations to the Minister of Health and Social Services as to whether or not a particular medication should be publicly funded. Assessments by INESSS focus on therapeutic value, cost-effectiveness (compared with other drug options), unmet needs and the impacts of a listing on the public health budget. While also non-binding, INESSS recommendations play a critical role in guiding the final drug funding decisions of the Government of Quebec.

For more information, visit the INESSS website.

Drug Reimbursement

The final step to accessing treatments in Canada through public funding consists of two parts: the pan-Canadian Pharmaceutical Alliance (pCPA) and Product Listing Agreements (PLAs).

The pCPA conducts joint federal, provincial, and territorial negotiations in which member jurisdictions engage drug manufacturers to determine if a particular drug will be publicly funded, at what cost, and with which reimbursement criteria. If a negotiation is successful, a Letter of Intent (LOI) is issued. A drug company then takes that LOI to each of the public drug plans in Canada and uses it as the basis for finalizing a PLA – a legally binding agreement that will trigger publicly funded access to that treatment in the jurisdiction.

For more information, visit the pCPA website.

PATIENT AND CLINICIAN INPUT: A vital part of the CADTH and INESSS review processes is patient, caregiver, and clinician input. Both CADTH and INESSS post calls for input from patient organizations and clinician groups (for INESSS, individual members of the public can also submit input) when conducting reimbursement reviews. Patient and clinician groups are encouraged to share their experiences and perspectives on the disease, existing treatments, including the drug under review, as well as insights into unmet needs the drug under review addresses. The combined input from patients, caregivers and clinicians serves to inform the review processes at the two agencies.

The Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) provides input into HTA reviews for treatments in aplastic anemia, myelodysplastic syndromes, and paroxysmal nocturnal hemoglobinuria.

For more information, visit the CADTH Patient Group Input and Feedback page.

For more information, visit the CADTH Clinician Group Input and Feedback page.

For more information, visit the INESSS Public Input page.

Formal and Informal Advocacy to Support Access to Treatment

Numerous patient organizations, like AAMAC, across the country advocate on behalf of their communities around issues such as access to treatment. Many provide opportunities for people to share their experiences and opinions as treatments make their way through the approval and reimbursement processes across Canada. Such engagement can be divided between formal and informal advocacy opportunities.

As part of the structured drug approval and public reimbursement processes, the only formal opportunities for input from patients, caregivers and physicians are within CADTH and INESSS. Beyond formal advocacy, individuals and the groups or organizations who represent them can make their voices heard around an issue related to access to treatment in a variety of ways. Some examples of informal advocacy include meetings with elected officials and bureaucrats, letter-writing campaigns, petitions, and social media campaigns.

*For more **information about advocating for access to treatment**, please contact the Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC) at info@aamac.ca or 1-888-840-0039.*

10 | ACKNOWLEDGEMENTS

Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC would like to acknowledge the contribution of Dr. Monika Oliver, BSc MD FRCPC, Division of Apheresis Medicine, Division of Hematology, University of Alberta Hospital, for medically reviewing and editing this educational resource.

We would also like to express our gratitude to AAMAC's patient representative and EVERSANA for their support in preparing this educational resource.

11 | APPENDIX

Being diagnosed with a complex disease like PNH can be overwhelming and the learning curve can be steep. Below are some points to help you prepare for medical appointments and to ask your physician, if they are not addressed during your appointment.

Note: *These lists are compiled from the Canadian Association of PNH Patients, AAMAC and AAMDSIF websites*

Points to address with your physician if you have just been diagnosed with PNH:

1 Can you explain what PNH is?

2 How sure are you about the diagnosis of PNH?

3 Do I need any other tests before we can decide on treatment?

4 Can you explain the types of tests used to diagnose PNH?

5 How serious is my diagnosis?

6 Do I need to see any other types of healthcare professionals?

7 What is my risk of blood clots?

8 Are there factors that could affect my outlook or treatment options?

9 What proportion of my overall blood cells consists of healthy cells as opposed to PNH-afflicted cells? Would you be able to tell me my 'PNH clone size'? What is the significance of this?

10 What should I watch out for when looking at my blood results?

11 Are there other disorders/diseases that are associated with PNH?

12 Is it contagious? Should I be concerned for those around me?

13 What is the expected impact of PNH on my life overall?

14 In case I feel ill, how would I understand if I must reach out to you or call 911?

15 Would you be able to connect me with other people dealing with PNH?

16 Should I be taking supplements like iron and folic acid? If so, how much and what are the risks/side effects?

17 Is it safe to get pregnant/have a baby if I have PNH? What do I need to know about the risks to ensure I have a healthy pregnancy?

18 What impact can PNH and any treatments I am taking have on my pregnancy?

Points to address with your physician when deciding on a treatment plan:

1 Is it possible to cure PNH?

2 How much experience do you have treating PNH?

3 Should I get a second opinion before starting treatment?

4 How many people have you treated for PNH?

5 Can you suggest a physician or Centre of Excellence?

6 What treatment choices do I have? Which treatment, if any, do you recommend, and why?

7 Do we need to treat the PNH right away?

8 What is the rationale behind recommending one treatment approach over another?

9 What is the expected timeframe for treatment to show effectiveness?

10 What should I do to be ready for treatment?

11 How long will treatment last? What will it be like? Where will it be done?

12 What is the method and schedule for administering the treatment?

13 What are the risks or side effects of the treatments that you recommend? How long are they likely to last?

14 How do we plan to address and alleviate the side effects?

15 Whom should I contact if I encounter side effects or complications?

16 Will treatment affect my daily activities?

17 What is the outlook for my survival?

18 What if the recommended treatment proves ineffective in my case?

19 Are there chances of symptom recurrence after an extended period of treatment?

20 Is it advisable for me to use an anticoagulant as a preventive measure against blood clots?

21 Is there a way to determine if my insurance includes the prescribed treatment?

22 Does the absence of private health insurance preclude me from accessing the recommended treatment?

23 Are there any clinical trials in Canada I ought to be aware of before deciding on a standard treatment?

24 What travelling is involved? I am (or I am not) able to travel far for a clinical trial.

25 Will I be treated any differently if I enrol in a trial?

26 What are the top research hospitals/centres for PNH trials?

27 Are there any benefits or risks associated with enrolling in a clinical trial?

28 Will you continue to oversee my care if I do enrol in a clinical trial?

Note: *Support groups and PNH experts do recommend an additional opinion when it comes to rarer blood disorders like PNH, as not all hematologists can be PNH specialists. This can also be helpful to gain access to a wider range of clinical trials.*

Points to address with your physician during and after treatment:

1 How will we know if the treatment is working?

2 What type of follow-up will I need during and after treatment?

3 How long does it typically take for treatment to start working?

4 Is there anything I can do to help manage side effects?

5 What symptoms or side effects should I tell you about right away?

6 Do I need to change what I eat during treatment?

7 Are there any limits on what I can do?

8 Should I exercise? What should I do, and how often?

9 What would my options be if the treatment isn't working?

10 Is there anything I can do to increase the chances of treatment working?

11 Can you suggest a mental health professional I can see to help me and my family adjust to this diagnosis?

12 Where can I find more information and support?

Top tips

1 Take a pen and paper and write your questions down.

2 A detailed summary is usually documented by the physician at every medical visit. While recording the consultation should not be necessary, if the physician is unable to provide this, with their permission, you can sometimes electronically record the consultation if you feel you cannot take all the information down.

3 We recommend you attend most consultations with a family member or friend, as it can be difficult to remember all that is said in a conversation.

4 Find a peer who has been diagnosed with PNH and understands what you're going through – ask your physician or search online for groups; you're not alone.

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This publication was made possible thanks to the support of:

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