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[14] Conclusion
Pulmonary arterial hypertension (PAH) is a rare form of pulmonary hypertension (PH) characterized by narrowing and stiffening of the pulmonary arteries, which ultimately results in heart failure. PAH affects individuals of all ages, all ethnicities and across all geographies. Although there is no cure for PAH, patient outcomes have improved considerably over the last 20 years with the advent of targeted therapies and growing experience of dedicated PH specialty centers. Despite ongoing additions to the treatment armamentarium, there remain substantial delays in the diagnosis and optimal care of patients with PAH as well as significantly delayed referrals to PH specialty centers. This remains the biggest barrier to maximizing patient outcomes, including increased survival and enhanced quality of life. By the time of confirmed diagnosis, many patients with PAH have already lost their jobs and are dependent on family. In clinical practice, early diagnosis and treatment (diagnosed while still within Functional Class I or II) has meant that patients can continue working throughout their treatment, perform light physical activity, and maintain greater independence.

Overcoming this barrier requires raising awareness among the general and medical communities and referring patients to PH specialists upon clinical suspicion of PAH. Due to the complexity of treating this life-threatening disease, the ongoing care of patients with PAH should be nothing short of a collaborative team effort between the patients’ primary care physician and a PH specialty center. Each stakeholder group — patient, physician, caregiver, allied health professional — can make important contributions toward maximizing patient outcomes. Organizational efforts through the Pulmonary Hypertension Association (PHA) can make this possible.

PHA has created a true spirit of cooperation among patients, physicians, nurses, scientists, caregivers, and industry — it has built a very large village — in order to find ways to prevent and cure PH, and to provide hope for the PH community through support, education, advocacy and awareness. Since 1990, PHA has evolved into a community of well over 10,000 patients, caregivers, family members and medical professionals and has become an international hub for the community. As this community expands internationally to developing nations where there is limited availability of treatments, lack of reimbursement, and resulting poor survival outcomes, PHA has the opportunity to make a significant impact in the lives of patients globally.
A Rare and Elusive Disease

Pulmonary hypertension (PH) is a general term used for any condition that causes abnormally high pressure in the pulmonary vascular system. PH is divided into five clinical groups depending on the cause of the condition (Appendix A: Clinical Classification of PH). Group 1, known as pulmonary arterial hypertension (PAH), is a rare form of PH that specifically affects the pulmonary arteries of the lungs, causing them to become narrow and stiff.

Pulmonary arteries carry blood that has returned from the body to the lungs, where the blood receives a fresh supply of oxygen. Narrowing of the arteries forces the right side of the heart to work harder to pump blood through the arteries and into the lungs (Figures 1 and 2), and can be caused by different mechanisms:¹

- **Vasoconstriction.** The muscles within the arterial walls contract, or squeeze;
- **Remodeling.** The arterial walls may thicken from too much cell growth in the lining of the vessels;
- **Inflammation;**
- **Thrombosis.** Tiny clots may form within the arteries.

Most people have not heard of the rare disease pulmonary arterial hypertension, let alone know the symptoms or understand the huge struggle that patients living with the disease face every day, such as simply climbing stairs.

*Gerry Fischer, President, PHA Europe*

Over time, the heart weakens and struggles to deliver oxygen to the body, resulting in the symptoms of PAH, including shortness of breath, fatigue, chest pain, dizziness and fainting.² If left untreated, the heart will eventually fail, leading to severe disability and death.³ There is no cure for PAH. However, treating patients early can control the disease for years.

**Risk Factors**

There are 30–50 cases of PAH per million individuals and the disease affects people of all ages, all ethnicities and across all geographies.⁴ Over the past three decades, the age and gender distribution of PAH has evolved. In the 1980s, the mean age of diagnosis was 36 years according to the National Institutes of Health registry.⁵ Today, the mean age of diagnosis is 50 years according to both French and U.S. registries.⁶ However, in developing countries such as China, the mean age of diagnosis remains 36 years.⁷ In addition, women are four times more likely to be affected than men. In the mid-1980s, the female-to-male ratio for idiopathic PAH (IPAH) was 1.7:1 as reported by the NIH Registry of IPAH; today it is 4.1:1 as reported by the REVEAL registry.⁸ However, there are geographic differences in these ratios. For example, a French registry reported a 1.9:1 female-to-male ratio for the years 2002-2003 and a Chinese registry reported a 2.4:1 ratio in 2007.⁹,¹⁰ The reason for these differences remains unknown; however, the role of hormones in the pathogenesis of PAH is under consideration because of the increased use of hormone replacement therapy in the US between the time of the NIH and REVEAL registries.¹¹

There are several types of PAH, each
Figure 1 – Normal heart compared with the heart of a patient with pulmonary hypertension.

Figure 2 – Narrowing of the pulmonary arteries associated with PAH.

PAH: Recommendations for Improving Patient Outcomes

of which is defined by a known cause (Figure 3). Idiopathic PAH (IPAH), formerly called primary pulmonary hypertension (PPH), corresponds to sporadic disease without a family history or an identified risk factor — no known cause. Heritable PAH corresponds to inherited genetic mutations in genes encoding members of the transforming growth factor β superfamily, including bone morphogenetic protein receptor type 2 (BMPR2), activin receptor-like kinase type 1, and endoglin. There are also clinical familial cases without identified germline mutations within these genes. Between 50 to 70 percent of patients with heritable PAH have mutations within the BMPR2 gene, which is known to help regulate the growth of cells in the walls of the small arteries of the lungs. It is important to note that other factors are also required to produce disease in these patients because only 20 percent of individuals with BMPR2 mutations develop PAH. Genetic testing is a very personal decision and is not mandated in patients with IPAH or in familial cases. If genetic testing is performed, genetic counseling is necessary in order to be fully informed of the risks and benefits.

A number of drugs and toxins have been identified that can place individuals at higher risk of developing PAH, including the use of certain appetite suppressants (e.g., aminorex, fenfluramine, dexfenfluramine), toxic rapeseed oil, methamphetamines, cocaine or amphetamines, St. John’s Wort, chemotherapeutic agents, and some selective serotonin reuptake inhibitors (SSRI) during pregnancy (resulting in persistent PH of the newborn). PAH is also associated with other medical conditions such as connective tissue diseases (e.g., scleroderma and lupus), HIV infection, and congenital heart disease with cardiac shunts.

Screening individuals with any of these known risk factors is critical for early diagnosis. Although there is no cure, the advent of targeted therapies has changed PAH from a rapidly fatal disease to a serious but treatable condition. Approximately 50 percent of people diagnosed with PAH die within five years. For people whose PAH is not treated, average survival is only about three years, making the need to obtain a rapid and accurate diagnosis all the
The nonspecific nature of symptoms, however, presents a considerable diagnostic challenge. The mean duration from symptom onset to a confirmed diagnosis by right heart catheterization is 2.8 years, and this delayed diagnosis has not improved in over two decades. Younger individuals (under the age of 36) and patients with a history of respiratory disorders, such as sleep apnea or obstructive airway disorder, are the most likely to experience a delayed diagnosis. It has been suggested that individuals under the age of 36 experience greater delays in diagnosis because they notice symptoms sooner due to having a more active lifestyle and are frequently diagnosed with asthma. They also make up the largest group of uninsured Americans.

The resistance to blood flow through the lungs (with resulting poor oxygenation) produces the symptoms of PAH, including dyspnea on exertion, fatigue, dizziness bending over or coughing, chest pain, syncope, hemoptysis, and edema. Over time, these symptoms get progressively worse and may severely impact a patient’s quality of life, making simple daily activities such as walking short distances difficult. Because these symptoms are nonspecific—and because PAH is such a rare disease—they are commonly attributed to other conditions such as asthma, chronic obstructive pulmonary disorder (COPD), chronic heart failure, being overweight and lack of fitness. As a result, most patients will see three different physicians over a three year period, on average, before they are finally diagnosed with PAH. Unfortunately, by this time, most patients are already at relatively advanced stages of disease—approximately 61 percent of patients are functional Class III and 12 percent are functional Class IV at the time of diagnosis.

<table>
<thead>
<tr>
<th>Class I</th>
<th>Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnea or fatigue, chest pain or near syncope.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest.</td>
</tr>
</tbody>
</table>
The trust that has evolved over the years between the physician, scientist, PHA and the patient has made it possible to conduct multicenter clinical trials … patients are willing to participate in clinical research and it contributes to advancement of knowledge in the field.

David Badesch, M.D.

Although non-invasive testing such as echocardiography and chest radiographs (X-rays) are useful in the detection of PAH, right heart catheterization (RHC) remains the diagnostic gold standard for PAH and is required to confirm a diagnosis (Appendix B: Summary of Common Tests for PH). RHC is an invasive procedure, involving the passing of a thin tube (catheter) through either the neck or groin and into the right side of the heart and arteries to measure the blood pressure and cardiac output. PAH is defined as an increase in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by RHC. Although RHC is used internationally to confirm a diagnosis of PAH, it is not used in all countries equally. In China, for example, only a few patients with severe PAH will undergo RHC due to the invasiveness and cost of the procedure.

Treatment
The outlook for patients with PAH has improved considerably in recent years with the growing number of treatment options. If patients are diagnosed and treated as early as possible—preferably while still Functional Class I or II—disease progression can be delayed, impacting both survival and quality of life. It is important to note, however, that a diagnosis of PAH must be confirmed with right heart catheterization prior to beginning treatment as these therapies can be harmful to patients who do not have PAH.

Treatments for PAH include conventional medical therapies (calcium channel blockers (CCBs), digoxin, diuretics, oxygen and warfarin) as well as targeted therapies. Importantly, CCBs can be used only in a small subset of PAH patients, whose pulmonary arteries significantly dilate during a vasoreactivity test. Such a test should be performed during RHC before treatment decisions are made. For patients not suitable for CCB treatment, or for those who deteriorate clinically despite treatment, three therapeutic classes of treatment that target key pathways involved in abnormal growth and contraction of the smooth muscle cells lining the pulmonary arteries in patients with PAH are currently available.
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Clinical Research

Twenty years ago, treatments for PAH did not exist. Today, thanks to advancements made in clinical research, there are nine treatments available. Of the roughly 7,000 known rare diseases, the FDA has approved just 400 treatments for 200 of these and PAH is tied with hemophilia for third (leukemia and HIV/AIDS are first and second, respectively) on this high priority list. There are also many more treatments in development. A search for “pulmonary arterial hypertension” on www.clinicaltrials.gov lists 455 active clinical studies world-wide. In just under a decade, PHA’s Research Program has committed over $9.5 million for research by leveraging partnerships with the National Heart, Lung, and Blood Institute (NHLBI), American Thoracic Society (ATS) and the American Heart Association (AHA), and PHA has supported more than 40 researchers through four independently reviewed cutting-edge research programs. These researchers are investigating new methods for early detection, new treatments to prevent the onset of PH, and ultimately trying to find a cure for this devastating disease.

In addition to funding research, PHA is actively involved in educating and recruiting patients for clinical trials. At PHA’s International Conference, which takes place every two years, a research room is hosted where everyone, including healthy individuals, is encouraged to give blood for clinical research.

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patients, caregivers, family members and medical professionals and has become an international hub for the community with more than 50 PH Associations worldwide (Appendix C: List of International PH Associations). As the organization has grown, it has stayed true to the vision of the founders:

*We continue to work every day to end the isolation that PH patients face, and find a cure for pulmonary hypertension.*

The strength of PHA lies in the strong sense of community and ownership among patients and medical professionals. There are co-equal roles among the various stakeholders within PHA (patients, clinicians, nurses, scientists and industry) and each stakeholder participates in ways that they are uniquely capable. Patients have a very high level of collaboration with the professional parts of the association. This sense of community empowers patients, allowing them to fight back against their disease and to become actively involved in its management. The physicians and scientists who are involved with PHA also understand that it is important to have those you are trying to help not be passive recipients of something that is done to them.

The PHA partnership model has greatly contributed to advancements in the diagnosis and management of PAH in part due to the trust that has evolved over the years between the physicians, scientists, and patients. This trust has made it possible to conduct successful multi-center clinical trials despite the fact that PAH is a rare disease. The patients, in fact, have the most important role within PHA and in many ways have directed not just how the organization works, but how the basic and clinical science has advanced in the field—by being organized and having a clear, consistent, strong message. The model that has been developed has begun to take hold in other organizations around the world. Collaboration among the global associations is helping to overcome some of the cultural and organizational differences between countries.

PHA also understands that if the learning stops so do patients’ lives. For this reason, there is a strong emphasis on education for medical professionals, patients, caregivers, political representatives, and support group leaders. PHA’s multi-sponsored, multi-pronged educational initiative is one of the most important ways that PHA has reached out to the medical and patient communities to improve disease awareness, early diagnosis and referral to PH expert centers in the form of international conferences and regional meetings, an online university, newsletters, medical journals, continuing medical education (CME), and a patient survival guide (Figure 5).

The PH community realizes that there is much that can be done to improve patient outcomes today until a cure is found. Given the rarity of the disease, one of the biggest barriers to maximizing outcomes, including increased survival and enhanced quality of life, are delays in the early diagnosis and optimal treatment of patients. Overcoming this barrier requires raising awareness among the general population and referring patients to PH specialists upon clinical suspicion of PAH. Organizational efforts through PHA can make this possible.
Maximizing Patient Outcomes

The outlook for patients with PAH has improved considerably in recent years with the introduction of diagnostic and treatment guidelines; however, the nonspecific nature of symptoms continues to make PAH a considerable diagnostic challenge. There remain substantial delays in the diagnosis and optimal care of patients with PAH as well as significantly delayed referrals to PH specialty centers. The time to diagnosis has not improved in over two decades. By the time of diagnostic right heart catheterization, many patients have become so functionally deteriorated that they have lost their jobs and are dependent on family—a very serious economic consequence. In clinical practice, early diagnosis (while still within Class I and II) has meant that patients can continue working throughout their treatment.

In addition to delayed referral, many PH specialists agree that there is also a noticeable dilution of patient management away from PH specialists and into the community. This may be due, in part, to the increasing number of orally available treatments for PAH, resulting in seemingly easier handling of these patients by non-PH specialists. There is naturally a desire by physicians to maintain the controlling hand in patient management and a reluctance to send patients off to another physician for their care for any variety of reasons. However, it is important to overcome this barrier from both sides by recognizing that patient management is nothing short of a team effort. Due to the complexity of treating this life-threatening disease, the care of patients with PAH should be nothing short of a collaborative team effort between the patients’ primary care physician and a PH specialty center (Figure 6).

PH specialists have the most experience managing PAH patients and the most expertise with PAH-specific drugs, such as calcium channel blockers (CCBs), prostacyclins, endothelin receptor antagonists and phosphodiesterase-5 inhibitors. The PAH team may also be conducting clinical trials that offer new alternatives or additive investigational PAH therapies, which may require simultaneous initiation with available and already approved treatment. Because all of these therapies require expertise in PAH, it is recommended that only PH specialty centers

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**Figure 6 – Collaborative Care Model with PH Specialty Centers: Initial and Ongoing Care**
initiate these treatments. Patients with suspected PAH should have their doctors perform diagnostic testing based on their suspicion for PAH. If an echocardiogram or respiratory function testing suggests PAH, or is confirmed by right heart catheterization, the treating physician should refer the patient to a PH specialist.

There are a number of adverse outcomes associated with the dilution of care away from PH specialty centers. PH specialty centers are critically important for treating and finding a cure for PAH through their involvement with clinical trials and registries. When patients are treated in the community, they typically are no longer available for database and registry information and do not access valuable clinical trials. Patients with PAH being treated in the community have fewer opportunities to meet fellow patients with PAH, and thus may lose out on valuable support throughout their disease. Finally, due to difficulties in the differential diagnosis of PH, some patients who are suffering from other forms of PH (besides PAH) may be misclassified and mistreated, losing important opportunities such as surgical treatment of chronic thrombo-embolic PH or early listing for lung transplantation in pulmonary veno-occlusive disease (PVOD).

The follow-up care of patients receiving PAH-specific therapies should include both visits to the patients’ primary care physician and periodic evaluations by the PH specialist in a collaborative approach. The frequency of visits should be individualized according to the patient’s specific clinical condition (suggested every three to six months), and it is also advisable to involve a local cardiologist or pulmonologist in the patient’s care.

Figure 6 – Collaborative Care Model with PH Specialty Centers: Initial and Ongoing Care
A Call to Action

Reducing the time to a confirmed diagnosis and referring patients to PH specialists for treatment are critical for maximizing patient outcomes, along with finding a cure through clinical research. In order to achieve this goal, it remains vital to raise disease awareness, especially among the general population and physicians, including primary care physicians/general practitioners, cardiologists, rheumatologists, immunologists, and obstetrician-gynecologists (ob-gyn). These key stakeholders are at the front lines of early diagnosis. However, everyone can contribute to the early diagnosis and treatment of PAH; below is a list of recommendations for each stakeholder group.

Pulmonary Hypertension Association
PHA has been a main driver in the advancement of our understanding of PAH, and these educational, research and awareness efforts must continue until a cure for PAH is found.

- Continue multi-sponsored, multi-pronged educational initiatives aimed at improving disease awareness, early diagnosis and referral to PH expert centers
- Conduct targeted global awareness campaigns targeting the general population and non-PH specialists
- Move forward legislative agendas for research funding
- Initiate conversation with various communities — patient, caregiver, medical — with the goal of developing educational programs

Patients & Caregivers
Empowered patients and caregivers drive physicians and their medical care decisions. Patients must be made aware that management of their life-threatening disease should be a collaborative effort between their local physician and a PH specialty team. Patients can contribute to finding a care and raising disease awareness in many ways.

- Enroll in clinical trials
- Get involved in PHA, take part in support groups and lobbying efforts for research funding
- Hold local meetings to help educate the general population about, and raise awareness of, PAH

Non-PH Specialists
 Patients will first present with symptoms to a non-PH specialist (primary care physician, ob-gyn, general cardiologist, pulmonologist or rheumatologist). Therefore, it is important that non-PAH specialists remain aware of PAH, understand that patients should be treated by a PH specialist only, and remain informed on how to handle patients upon clinical suspicion.

- Awareness of PAH as a differential and understanding of diagnostic tests (and interpretation of results) for PAH
- Understand the importance of diagnosing PAH as early as possible
- Remain aware of the closest PH specialty centers for referral, which is available on the PHA website (Appendix C)
- Refer patients to PH specialists upon clinical suspicion of PAH based on symptoms and signs, or typical findings on chest X-ray, ECG, echocardiography or laboratory tests (elevated BNP levels)
- Partner with PH specialists in the management of
Conclusion

The outlook for patients with PAH has improved considerably in recent years with increasing experience of specialty PH centers and the growing number of treatment options. With earlier diagnosis and treatment—preferably while patients are still Functional Class I or II—disease progression can be delayed, impacting both survival and quality of life. Thus, the need to obtain a rapid and accurate diagnosis is highly imperative for both patients and physicians. PHA has been a main driver in the advancement of our understanding of PAH, and these educational, research and awareness efforts must continue until a cure for PAH is found. Every stakeholder group—PH specialists, physicians, patients, caregivers, allied health professionals—has a role to play in meeting this challenge. Together, we can improve the outcome of patients by raising disease awareness among the general and medical communities and supporting clinical trials and registries in our efforts to find a cure.
APPENDIX A:
Clinical Classification of Pulmonary Hypertension

1 Pulmonary arterial hypertension (PAH)
   1.1 Idiopathic PAH
   1.2 Heritable
      1.2.1 BMPR2
      1.2.2 ALK1, endoglin
      1.2.3 Unknown
   1.3 Drug- and toxin-induced
   1.4 Associated with
      1.4.1 Connective tissue diseases
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 Congenital heart diseases
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia
   1.5 Persistent pulmonary hypertension of the newborn
1’ Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2 Pulmonary hypertension owing to left heart disease
   2.1 Systolic dysfunction
   2.2 Diastolic dysfunction
   2.3 Valvular disease
3 Pulmonary hypertension owing to lung diseases and/or hypoxia
   3.1 Chronic obstructive pulmonary disease
   3.2 Interstitial lung disease
   3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   3.4 Sleep-disordered breathing
   3.5 Alveolar hypoventilation disorders
   3.6 Chronic exposure to high altitude
   3.7 Developmental abnormalities
4 Chronic thromboembolic pulmonary hypertension (CTEPH)
5 Pulmonary hypertension with unclear multifactorial mechanisms
   5.1 Hematologic disorders: myeloproliferative disorders, splenectomy
   5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis:
      lymphangioleiomyomatosis, neurofibromatosis, vasculitis
   5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
## APPENDIX B:
Common Tests for Pulmonary Hypertension

### Imaging (Noninvasive) Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>X-ray is used to determine if pneumonia or lung scarring is present, if the heart and pulmonary arteries are enlarged, and if there is fluid in the lungs.</td>
</tr>
<tr>
<td>V/Q scanning</td>
<td>Ventilation/Perfusion (V/Q) scanning is a special test that uses radioactive materials to look for blood clots in the lungs. A normal scan effectively excludes clots in the lungs.</td>
</tr>
<tr>
<td>CT (CAT) scanning</td>
<td>A CAT scan is a special X-ray of the body that provides images that a chest x-ray could not. It is used to examine the heart and lungs in greater detail, and potentially to look for blood clots in the lungs.</td>
</tr>
</tbody>
</table>

### Invasive Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac catheterization</td>
<td>Right Heart Catheterization (RHC) is the “gold standard” test for confirming a diagnosis of PAH. A catheter is placed into the veins and advanced into the pulmonary arteries to measure pressure in the right side of the heart and the lungs, and cardiac output (the amount of blood that the heart pumps).</td>
</tr>
<tr>
<td>Pulmonary angiogram</td>
<td>Pulmonary angiogram is the “gold standard” test to identify blood clots in the lungs. A dye is injected into the pulmonary arteries while X-ray pictures are taken.</td>
</tr>
</tbody>
</table>

### Laboratory Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Test:</td>
<td></td>
</tr>
<tr>
<td>- Electrolytes</td>
<td></td>
</tr>
<tr>
<td>- Kidney Function</td>
<td></td>
</tr>
<tr>
<td>- Liver Function</td>
<td></td>
</tr>
<tr>
<td>- Thyroid Function</td>
<td></td>
</tr>
<tr>
<td>- ANA - Antinuclear antibody</td>
<td>A screening test for suspected connective tissue (autoimmune) disease</td>
</tr>
<tr>
<td>HIV Test</td>
<td></td>
</tr>
<tr>
<td>BNP</td>
<td>Brain natriuretic peptide (BNP) is a small protein made by the heart; elevated levels may suggest development or presence of pulmonary hypertension and right ventricular impairment.</td>
</tr>
</tbody>
</table>

### Exercise Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Minute Walk Test</td>
<td>This test measures how far a person can walk in 6 minutes and is used to provide an estimate of exercise capacity.</td>
</tr>
<tr>
<td>Treadmill Test</td>
<td>This test measures how long a person can walk on a treadmill with increasing speed and incline and is a more formalized way to determine exercise capacity.</td>
</tr>
<tr>
<td>Cardiopulmonary Exercise Testing</td>
<td>These measurements of heart function and lung gas exchange (oxygen, carbon dioxide) are performed while exercising on a treadmill or bicycle.</td>
</tr>
</tbody>
</table>
### Imaging

- **Chest X-ray**
  - Used to determine if pneumonia or lung scarring is present, if the heart and pulmonary arteries are enlarged, and if there is fluid in the lungs.

- **V/Q scanning**
  - Ventilation/Perfusion (V/Q) scanning is a special test that uses radioactive materials to look for blood clots in the lungs. A normal scan effectively excludes clots in the lungs.

- **CT (CAT) scanning**
  - A CAT scan is a special X-ray of the body that provides more detailed images than a chest x-ray. It is used to examine the heart and lungs in greater detail, and may also be used to look for blood clots in the lungs.

- **Cardiac magnetic resonance imaging (MRI)**
  - Cardiac MRI is an imaging technique that can accurately measure right ventricular chamber volumes and function.

- **Echocardiogram**
  - An echocardiogram provides an ultrasound of the heart. It is used to take pictures of the heart muscle, heart valves, and to estimate pulmonary artery (PA) pressure.

### Invasive Tests

- **Cardiac catheterization**
  - Right Heart Catheterization (RHC) is the “gold standard” test for confirming a diagnosis of PAH. A catheter is placed into the veins and advanced into the pulmonary arteries to measure pressure in the right side of the heart and the lungs, and cardiac output (the amount of blood that the heart pumps).

- **Pulmonary angiogram**
  - Pulmonary angiogram is the “gold standard” test to identify blood clots in the lungs. A dye is injected into the pulmonary arteries while X-ray pictures are taken.

### Laboratory Testing

- **Blood Test:**
  - Electrolytes
  - Kidney Function
  - Liver Function
  - Thyroid Function
  - ANA - Antinuclear antibody, a screening test for suspected connective tissue (autoimmune) disease

- **HIV Test**

- **BNP**
  - Brain natriuretic peptide (BNP) is a small protein made by the heart; elevated levels may suggest presence of impaired right ventricular function.

- **N-BNP**
  - N-terminal brain natriuretic peptide — Parent protein for BNP; circulates in the blood in higher levels than BNP and elevated levels may also signal presence of pulmonary hypertension and right ventricular impairment.

### Pulmonary Function Testing

These are breathing tests to determine airway (lung) function.

### Electrocardiogram (EKG)

EKG is a noninvasive measurement of electrical activity in the heart that examines for heart damage and/or abnormal heart rhythms.

### Cardiopulmonary Exercise Testing

These measurements of heart function and lung gas exchange (oxygen, carbon dioxide) are performed while exercising on a treadmill or bicycle.
## APPENDIX C:
Global PH Associations

### North and Central America

<table>
<thead>
<tr>
<th>Association Name</th>
<th>Acronym</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Hypertension Association</td>
<td>PHA</td>
<td>United States</td>
</tr>
<tr>
<td>Puerto Rican PH Support Group</td>
<td></td>
<td>Puerto Rico</td>
</tr>
<tr>
<td>Sociedad Latina de PH</td>
<td>SLHP</td>
<td>United States</td>
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<tr>
<td>Pulmonary Hypertension Association of Canada</td>
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<tr>
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<tr>
<td>Edmonton Alberta Pulmonary Hypertension Support Group</td>
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<td>Pulmonary Hypertension Society of Ontario</td>
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<td>Toronto Chapter, PHA Canada</td>
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<td>University of British Columbia Pulmonary Hypertension Society</td>
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<tr>
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<td>AMHAP</td>
<td>Mexico</td>
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<tr>
<td>Fundación de Apoyo para la Hipertensión Pulmonar del Sureste, AC</td>
<td>FAHIP</td>
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### Europe

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<th>Acronym</th>
<th>Country</th>
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<tbody>
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<td>Pulmonary Hypertension Association of Austria</td>
<td>PHA Austria</td>
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<tr>
<td>Pulmonale Hypertensie vzw Belgie</td>
<td>Belgium PH vzw</td>
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<tr>
<td>HTAP Belgique</td>
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<tr>
<td>Pulmonary Hypertension Association of Bulgaria</td>
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<tr>
<td>Sdružení Pacientů s Plicní Hypertenzí</td>
<td>SPPH</td>
<td>Czech Republic</td>
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<tr>
<td>Pulmonary Hypertension Association of Europe</td>
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<td>Hypertension Arterielle Pulmonaire France</td>
<td>HTAP France</td>
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<tr>
<td>Pulmonare Hypertonie e.V</td>
<td>PHeV</td>
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<td>AIPi</td>
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<tr>
<td>Associazione Malati Ipertensione Polmonare</td>
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<td>Italy</td>
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<td>Pulmonary Hypertension Association of Nederland</td>
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<tr>
<td>Pulmonary Hypertension Association of Norway</td>
<td>PHA Norway</td>
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<td>RESPIRAR-APHP</td>
<td>Portugal</td>
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<td>Asociația Hipertensiunea Arterială Pulmonară din România</td>
<td>PHA Romania</td>
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<tr>
<td>Asociación Nacional de Hipertensión Pulmonar</td>
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<td>SPHV</td>
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<tr>
<td>Pulmonary Hypertension Association UK</td>
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### Middle East

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<th>Association Name</th>
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<tbody>
<tr>
<td>Saudi Advisory Group on Pulmonary Hypertension</td>
<td>SAPH</td>
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<tr>
<td>Israel Pulmonary Hypertension Association</td>
<td>PH Israel</td>
<td>Israel</td>
</tr>
<tr>
<td>Pulmoner Hipertansiyon Derneği</td>
<td>PHA Turkey</td>
<td>Turkey</td>
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### Australia

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<tr>
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<tbody>
<tr>
<td>Pulmonary Hypertension Association of Australia</td>
<td>PHA Australia</td>
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<tr>
<td>PH New South Wales</td>
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<tr>
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### Asia

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<tbody>
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<td>Pulmonary Hypertension Association of Japan</td>
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<tr>
<td>Singapore PH Support Group</td>
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<tr>
<td>Taiwan Foundation for Rare Disorders</td>
<td>TFRD</td>
<td>Taiwan</td>
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### South America

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<tr>
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<tbody>
<tr>
<td>Hipertensión Pulmonar Argentina</td>
<td>HIPUA</td>
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<tr>
<td>PHA Argentina</td>
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<tr>
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<td>Brazil</td>
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### Africa

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<tr>
<td>Pulmonary Hypertension Association of South Africa</td>
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</table>
References

3 Ibid
9 Ibid
13 Ibid
14 Ibid
16 Ibid
21 Ibid
22 Ibid

23 Ibid


