

Research Priorities for Future Pulmonary Hypertension Research: Your Input Leads to Your Impact

Although millions of dollars are spent every year on research to develop new ways to diagnose and treat the various causes of PH, progress in medical research is often slow and incremental. More PH research will always be needed, and more funds will be required to conduct it. Because the resources to fund and conduct research are limited, it would be helpful to know which problems are most important to patients. Who better to guide doctors and researchers on where to focus their efforts than those most directly impacted by PH? To understand what questions and problems should be prioritized for future PH research, we decided to ask you!

What is a research Priority Setting Partnership?

There is an established method of setting research priorities. A non-profit organization in the United Kingdom called the James Lind Alliance (JLA) developed an approach to engaging patients, caregivers, and clinicians to determine research priorities. This approach has been applied to over 100 diseases and conditions to date. More information about the JLA is available on their website at www.jla.nihr.ac.uk. With a group of Canadian PH specialists, PH patients, and other experts, we embarked on a PH Priority Setting Partnership project aligned with the JLA guidance. The Canadian PH Priority Setting Partnership was funded by the Canadian Institutes for Health Research and the Libin Cardiovascular Institute at the University of Calgary. Our initial aim was to understand your questions and priorities for future research that the Canadian Pulmonary Hypertension Registry (CPHR) could study. This project's scope quickly expanded, and we decided to do all types of research related to any aspect of PH.

What were the results of the Canadian PH Priority Setting Partnership?

Despite significant challenges related to the COVID-19 pandemic, and thanks to the incredible support of PHA Canada and HTAPQ, we were able to complete the Priority Setting Partnership in 2022. To start, we engaged over 240 individuals across Canada with an online survey. The surveys were distributed by PHA Canada and HTAPQ in both English and French. We asked what questions you had related to the causes and risk factors, diagnosis, treatment and management, and prognosis of PH. We received over 1,800 responses which were grouped into similar ideas. Based on our interpretation, and in consultation with our patient partners, the initial survey responses were rephrased as 187 unique *researchable* questions that could be addressed by research. We found that good answers already existed for 30 of these questions. So, we next asked the PH community to rank the remaining 157 questions in a second survey. The second survey's top 25 most frequently chosen questions were discussed during a two-day online workshop in February 2022. The workshop included patients, family members and caregivers, and PH specialists from across Canada. At the end of this workshop, we arrived at a top 10 list of questions for future PH research ranked by importance (see Table).

As you can see, there is a broad range of questions in the Top 10 and Top 25, and the Top 3 questions were unanimous. The number one priority is related to the underlying mechanisms that cause PAH. This is important because the development of new treatments usually depends on a deep understanding of why a disease develops (i.e., the mechanism). The second highest priority question addressed the need for therapies that can reverse PAH. Current treatments stabilize and slow down the disease but do not

reverse the abnormal changes in the arteries of the lungs. Therapies that reverse abnormalities in lung arteries may be the next best step to a cure. The third top priority addressed precision medicine. More specifically, precision medicine means finding accurate ways of choosing which drug or combinations of drugs will work best for an individual patient. For more details, this priority-setting partnership project has now been published in the Journal of Heart and Lung Transplantation, a leading medical journal in the field of PH. The full manuscript is available online at [https://www.jhltonline.org/article/S1053-2498\(22\)02160-X/fulltext](https://www.jhltonline.org/article/S1053-2498(22)02160-X/fulltext). Your Priority Setting Partnership results were also presented to the global PH community at the European Respiratory Society conference in September 2022 to get the word out as broadly as possible.

What does this Priority Setting Partnership mean for future PH research in Canada and worldwide?

Thanks to your input and this Top 10 list, patients and caregivers have an influence on which PH research gets funded in the next few years. Because of the limited dollars available for research, many good ideas and applications do not get funded. For example, only about 15% of health research projects' applications are funded by Canada's main health research funding body, the Canadian Institutes for Health Research. When researchers write grant applications to ask for money to perform their research, they often engage patient partners to provide their perspectives on the importance of the proposed research. Now, researchers can also explain in their grant applications how their research idea directly addresses one or more of the priorities of the entire PH community. These are priorities you helped create and shape. The impact of this is not limited to Canada but can be referred to and cited by researchers all over the world.

Additionally, researchers can still see the long list of 157 unanswered questions you helped create, which may inspire them with new ideas to tackle in their future research. Several pharmaceutical companies are invested in PH, and they may also consider how their research and development align with your priorities. Ultimately, the Canadian PH Priority Setting Partnership Top 10 list provides a roadmap for future PH research, but off-road travel is always encouraged!

Where do we go from here?

We will periodically evaluate how this list is being used in the coming years. Are projects funded in Canada aligned with these topics? Is the Top 10 list cited by researchers in grants and peer-reviewed research papers? There is also more work to be done as some areas of PH research and types of PH were not addressed in this project. This does not mean such groups are not important or won't be addressed by future research. Rather, other PH groups may require their own dedicated priority-setting partnerships. For example, our team consisted of experts in adult PH, not pediatric PH. We were also concerned that important questions relating to pediatric PH would be diluted by questions from the much larger adult PH community. Therefore, questions about pediatric PH were not included in this project's scope. Given the unique challenges faced by kids with PH and their families, we propose and highly encourage a dedicated priority-setting exercise for future research on pediatric PH.

In conclusion, I extend sincere thanks to all who participated in the project and to all who will use its results.

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Table (For design, ideally use all 25, if space is an issue, create a table with the top 10)

Title: Top 25 priorities for future pulmonary hypertension research

Rank from Final Workshop	Question
1	What are the specific mechanisms that lead to the development of pulmonary arterial hypertension (PAH)?
2	How can pulmonary hypertension (PH) be reversed or put into remission, and how can we measure disease modification or reversal clinically?
3	How can we predict which treatment or combination will work best for an individual PH patient (e.g., personalized medicine)?
4	What are the mechanisms of right heart adaptation to PH and right heart failure?
5	Which interventions or treatment strategies result in the best outcomes for patients with PH?
6	What is the role of the immune system and auto-immunity in the development of PAH, and can treatments directed at the immune system help with PAH?
7	What are the best tools to predict progression of PH and how fast the disease will progress?
8	What is the most effective and safe amount of exercise training for PH patients?
9	Are there biomarkers that allow early detection of PH?
10	Are stem cell therapies effective and safe for treating PH?
11	What is the underlying cause of idiopathic PAH?
12	What are the mechanisms by which cardiac function continues to deteriorate despite an improvement in symptoms?
13	When a PH patient needs surgery, what are the best anesthetic approaches and if general anesthesia is required, which anesthetics are safest?
14	How can we detect when the disease process (PH) starts, and how long does it take for symptoms to develop after it starts?
15	What are the long-term consequences and complications in PH patients who are long-term survivors?
16	How can the delay to diagnosis of PH be reduced?
17	For how long is PH treatment effective, and will the effect wear off with time?
18	Is there a relationship between iron deficiency and the development or progression of PAH, and if so, does the treatment of iron deficiency improve outcomes?
19	Can exercise testing be used to identify early PH and predict the risk of developing PH in the future?
20	How can the side effects of PH therapies be managed or reduced?
21	What is the most accurate method to classify the severity or risk of a patient with PH?
22	Are there any harmful long-term effects of medications used for PH?

23	How can universal coverage for all PH medications be ensured in Canada?
24	Can educational interventions targeted at clinicians in training, primary care, and second-line (e.g., specialist) clinicians improve awareness of PH and lead to earlier diagnosis of PH?
25	How do COVID-19 and COVID-19 vaccinations affect people with PH?