Recommendations from the Massachusetts Task Force on Pulmonary Hypertension

June 14, 2021

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PULMONARY HYPERTENSION TASK FORCE STATUTORY LANGUAGE

Section 16Z of Chapter 6A of the Acts of 2017: Pulmonary Hypertension Task Force

Section 16Z. (a) Notwithstanding any general or special law to the contrary, the executive office of health and human services shall establish a pulmonary hypertension task force. The task force shall consist of: the secretary of the executive office of health and human services or a designee, who shall serve as chair; the commissioner of the department of public health or a designee; the commissioner of insurance or a designee; the director of Medicaid or a designee; and 7 persons to be appointed by the secretary of the executive office of health and human services, 2 of whom shall be representatives from the Massachusetts Medical Society Alliance, Inc. appointed in consultation with their relevant specialty chapters, 1 of whom shall be a representative from the Massachusetts Association of Health Plans, Inc., 1 of whom shall be a representative from commercial health insurance plans or managed care organizations doing business in the commonwealth, 1 of whom shall be an individual with a diagnosis of pulmonary hypertension, 1 of whom shall be a representative of a pharmaceutical company that manufactures a drug or device for detecting, preventing or treating pulmonary hypertension and 1 of whom shall be a representative of a research, advocacy or support organization primarily serving individuals with a diagnosis of pulmonary hypertension.

(b) The task force shall: (1) develop and annually update a summary of the advances made in research on and treatment and diagnosis of pulmonary hypertension; (2) develop and annually update a summary of the advances made in access to care for individuals with a diagnosis of pulmonary hyp ertension; (3) monitor pulmonary hypertension research, services and support activities across the commonwealth, including coordination of the commonwealth's activities and programs with respect to pulmonary hypertension; (4) develop and annually update a comprehensive strategic plan to improve health outcomes for individuals with a diagnosis of pulmonary hypertension, including recommendations to: (a) advance research or pulmonary hypertension; (b) improve the transplantation criteria and process concerning lung and heart-lung transplants for individuals with a diagnosis of pulmonary hypertension; (c) improve public awareness and recognition of pulmonary hypertension; (d) improve health care delivery for individuals with a diagnosis of pulmonary hypertension; (e) improve the early and accurate diagnosis of pulmonary hypertension; and (f) systematically advance the full spectrum of biomedical research on pulmonary hypertension; and (5) develop and annually update the progress made in implementing such comprehensive strategic plan.

(c) The task force shall submit its recommendations to the governor and the clerks of the house of representatives and senate annually not later than December 31.

MEMBERS OF THE MASSACHUSETTS PULMONARY HYPERTENSION TASK FORCE

Name	Representing
Lindsey Tucker	Secretary of Health and Human Services
Anita Christie	Commissioner of Department of Public Health
Vacant	Commissioner of Division of Insurance
Monica Le, MD	Director of Medicaid
Aaron Waxman, MD, PhD	Massachusetts Medical Society Representative #1
Kimberly Fisher, MD	Massachusetts Medical Society Representative #2
Patricia Toro, MD	Massachusetts Association of Health Plans
Vacant	Commercial Insurance or Managed Care Organization
Ernesto Bencosme	Individual diagnosed with pulmonary hypertension
Gil Golden, MD, PhD	Pharmaceutical company
Frank Cann	Research, advocacy, or support organization

SECTION 1: LIST OF RECOMMENDATIONS

Statute charges the task force with developing and annually updating a comprehensive strategic plan to improve health outcomes for individuals with a diagnosis of pulmonary hypertension.

This list of recommendations and the final report were finalized in April of 2021 after being delayed as a result of team members on the Task Force being redirected to the COVID response efforts. A summary of recommendations is below, and detailed recommendations can be found in Section 3.

Charge 4a. Advance research on pulmonary hypertension

Recommendation: Promote and increase patient participation in pulmonary hypertension-related clinical trials through education and patient-to-patient support programs.

Charge 4b. Improve the transplantation criteria and process concerning lung and heart-lung transplants for individuals with a diagnosis of pulmonary hypertension

Recommendation 1: Change state policy related to organ donation from the current "opt in" to an "opt out" approach also known as *presumed consent*.

Recommendation 2: Continue awareness and educational initiatives for the general public to increase organ donation rates.

Recommendation 3: Provide a mechanism for patient, advocacy group, and stakeholder involvement in identifying critical transplantation needs.

Recommendation 4: Explore mechanisms to better identify high- and low-risk pulmonary arterial hypertension patients and to track patient-reported outcomes beyond early survival metrics.

Charge 4c. Improve public awareness and recognition of pulmonary hypertension

Recommendation 1: Promote Massachusetts based pulmonary hypertension events through the engagement of multiple paid, paper, and social media outlets.

Recommendation 2: Distribute accurate and publicly available resources to primary care offices and settings for placement in waiting rooms and patient exam rooms.

Recommendation 3: Develop and implement a statewide public awareness campaign designed to reach people outside of traditional health care settings.

Charge 4d. Improve health care delivery for individuals with a diagnosis of pulmonary hypertension

Recommendation: Explore strategies to improve patient care coordination between primary care physicians and pulmonary hypertension specialists.

Charge 4e. Improve the early and accurate diagnosis of pulmonary hypertension

Recommendation: Provide education and training to build the capacity of primary care providers to understand pulmonary hypertension and improve early diagnosis and treatment.

Charge 4f. Systematically advance the full spectrum of biomedical research on pulmonary hypertension

See recommendations for Charges 4a and 4b.

Of the recommendations in this report, the following two recommendations would have the greatest impact in the care of patients with pulmonary hypertension. They are:

- Charge 4b, Recommendation 1: Change state policy related to organ donation from the current "opt in" to an "opt out" approach also known as *presumed consent*. As a result of presumed consent, more donors will exist allowing an increase in the available organs for pulmonary hypertension patients requiring life-saving transplants.
- Charge 4e, Recommendation 1: Provide education and training to build the capacity of primary care providers to understand pulmonary hypertension to increase early diagnosis and treatment.

SECTION II: PULMONARY HYPERTENSION OVERVIEW

Pulmonary hypertension is a complex and often misunderstood disease. It is a type of blood pressure that affects the arteries in the lungs and the right side of the heart. It is not common but is a life threatening condition. It occurs when pressure in the blood vessels within the heart-to-lung system is unusually high, impacting an individual's blood flow and lowering the amount of oxygen in the blood. As the pressure builds, the heart's lower right chamber (right ventricle) must work harder to pump blood to the lungs, eventually causing the heart muscle to weaken and fail. Complications, potentially fatal, can include blood clots, arrhythmia (irregular heart rhythm), bleeding in the lungs, or coughing up blood. Pulmonary hypertension often develops in conjunction with other diseases, such as congenital heart disease, high blood pressure, liver disease, and chronic lung diseases.

There are five different groups (or types) of pulmonary hypertension, based on the disease's causes, manifestations, and mechanisms.
Group 1: Pulmonary arterial hypertension (PAH) results from a narrowing and stiffening of the lungs' arteries and is more common than the other groups. The Pulmonary Hypertension Association estimates that roughly 300,000 individuals nationwide have a diagnosis of pulmonary hypertension (PH). In Massachusetts, there are an estimated 1,200 PAH patients, and an unknown number of PH patients. Little information is available regarding pulmonary arterial hypertension's true impact on the population, because it is difficult to diagnose. There is no cure, but treatment can help lessen symptoms and improve quality of life.
Group 2: pulmonary hypertension due to left heart disease
Group 3: pulmonary hypertension due to lung disease and/or chronic hypoxia
Group 4: pulmonary hypertension due to blood clots in the lungs
Group 5: pulmonary hypertension due to blood and other disorders

In its early stages, the signs and symptoms of pulmonary hypertension might not be noticeable for months, or even years. As the disease progresses, symptoms become worse and can vary. Patients most commonly report experiencing shortness of breath and fatigue, as well as chest pain, fainting or light-headedness, and edema (swelling). Unfortunately, these same symptoms can be caused by other medical problems, such as asthma and chronic obstructive pulmonary disorder (COPD) that are more common. Therefore, it is difficult to diagnose pulmonary hypertension, and there can be long delays in diagnosis. Although pulmonary hypertension occurs at all ages, its incidence increases with age, and is more common among people aged 75 or older, women, and non-Hispanic blacks. It is essential for newly diagnosed patients to be referred to a pulmonary hypertension specialist who can accurately find what is causing their disease and develop treatment plans that address their specific group of pulmonary hypertension.

SECTION III: RECOMMENDATIONS WITH EXPLANATIONS

The following recommendations were developed over the course of four Pulmonary Hypertension Task Force meetings held between 2017 and 2019. They correspond to the legislation under Section 16Z (b) (4) and have been reviewed and approved by all task force members. See Attachment A: Summary of Advances Made in Research on Treatment and Diagnosis of Pulmonary Hypertension that was developed to inform task force discussion.

Charge 4a. Advance research on pulmonary hypertension

> Recommendation: Promote and increase patient participation in pulmonary hypertension-related clinical trials through education and patient-to-patient support programs.

Patient participation in clinical trials plays an important and critical role in pulmonary hypertension research. In addition to funding, patients are crucial for the implementation and success of pulmonary hypertension-related clinical trials. Enrollment in trials can be low, as patients often do not understand what participation involves.

An important source of information is the Clinical Trials website, a service of the US National Institutes of Health. It is a registry and results database of publicly- and privately-supported clinical studies of human participants from around the world and is available at https://clinicaltrials.gov. The Pulmonary Hypertension Association (PHA) website also provides clinical trial information and is available at https://pulmonaryassociation.org. (PHA is a national nonprofit organization based in education, support, advocacy, and research support.)

A first step is to increase patients' awareness and knowledge of what is involved in clinical trials. This would be accomplished by creating and distributing information and/or educational materials to pulmonary hypertension patients in efforts to help them to better understand the importance of participation in a clinical trial. These materials' messages would emphasize the importance of patient participation, their contribution to research, and becoming partners to advance medical breakthroughs, as well as patients' access to new treatments. Including messages to reduce barriers to participation caused by patient hesitance is important as well.

A second step is to develop peer-to-peer or patient-to-patient programs. These programs would connect a pulmonary hypertension patient with another pulmonary hypertension patient, or someone living with a rare disease, who is participating in a clinical trial. This kind of patient-centered program would provide education to address patient concerns and questions, and to offer support for pulmonary hypertension patients looking for guidance and feedback from others who are already participating in a trial.

Charge 4b. Improve the transplantation criteria and process concerning lung and heart-lung transplants for individuals with a diagnosis of pulmonary hypertension

Recommendation 1: Change state policy related to organ donation from the current "opt in" to an "opt out" approach also known as *presumed consent*.

Recommendation 2: Continue awareness and educational initiatives for the general public to increase organ donation rates.

Recommendation 3: Provide a mechanism for patient, advocacy group, and stakeholder involvement in identifying critical transplantation needs.

Recommendation 4: Explore mechanisms to better identify high- and low-risk pulmonary arterial hypertension patients and to track patient-reported outcomes beyond early survival metrics.

With improvements in the diagnosis and treatment of pulmonary arterial hypertension, survival rates have increased over time. However, for patients with severe disease who do not adequately respond to medical therapy, lung transplantation is an important option that confers substantial gains in long-term survival and quality of life. The long-term course of pulmonary arterial hypertension patients is often unpredictable. Even patients with severe disease can appear well, yet can deteriorate quickly and with out warning. Therefore, clinicians must remain vigilant to recognize patients who are deteriorating or not reaching therapeutic goals and ensure that they are referred for a transplant in a timely fashion. Lung transplantation requires a lengthy evaluation process that must be started in a timely manner for optimal outcomes. Significant strides have been made in all areas of lung transplantation to make its processes shorter, smoother, and more successful; however, there is still room for improvement.

Organ donation rates must be increased in conjunction with advancing lung transplantation research. Each year, the number of people on the transplant waiting list in the United States continues to be much larger than the number of available donors. Organ donation rates should be increased to meet the needs of Massachusetts residents, as well as across the US. While 95% of US adults support organ donation, only 58% are actually signed up as donors. (HRSA, 2019) The prevalence of misinformation and myths that contribute to people not becoming donors is one reason for this.

One way to increase donation rates is to examine state policy change regarding "opt out" rather than "opt in" approaches to organ donation. Also called presumed consent, this change assumes everyone is a donor unless stated otherwise or unless people remove themselves from the organ donation list. In the US, there have been efforts by several states in the last eight years to introduce "opt out" legislation (Colorado, Connecticut, Pennsylvania and Texas). Additionally, approximately 25 European countries have some version of "opt-out" organ donation. For example, Spain's model of an "opt out" policy expands the contexts in which organs are procured, which has significantly increased donor rates. Researchers are examining the effect these strategies have on donation rates.[1]

Continuing to increase awareness and knowledge among the general public about the importance of organ donation and how to register as a donor is important and vital to increase organ donation rates. The American Transplant Foundation established April as National Donate Life Month. This strategy

[1] *American Journal of Transplantation* information about Spain's model
https://www.eurekalert.org/pub_releases/2017-01/w-hsa010617.php

encourages people to register as donors and provides an optimum opportunity to spread awareness and show support.

With guidance from the state Advisory Council on Organ and Tissue Transplants and Donations, the Department of Public Health in collaboration with the New England Donor Services has implemented a community-based educational campaign to increase awareness and education among the general public about the importance of organ donation and the ease of registering as a donor. A recent phase of the campaign involved a three-month media buy using display ads and videos posted on Facebook, Google, and other online advertising venues. Posters are also displayed at RMV locations and hospitals. The PHA is also highlighting organ donation and is using active social media messaging efforts during National Donate Life Month to generate more awareness.[2]

Additional activities to expand the donor pool include active donor management (to determine if procurement can proceed) and considering lung procurement from donors who have suffered a cardiac, rather than brain, death. New technologies and mechanisms, such as ex vivo lung perfusion, are being used to explore the extent to which the donor pool can be expanded. The transplant community also continues to reassess and expand its donor selection criteria in order to maximize the possibility of transplantation.

Pertinent to PH patients' ability to receive lung transplants is the Lung Allocation Score system (LAS); this mechanism of organ prioritization has reduced waitlist times, endorses the most appropriate allocation of organs, and streamlines the overall process. It has become a critical component of transplant priority criteria, and has led to reduced mortality for those patients on wait lists. However, the LAS lacks the ability to distinguish between high- and low-risk pulmonary arterial hypertension patients, creating the opportunity for health care organizations to improve their systems for prioritizing transplant candidates. Additionally, the LAS system does not factor any patient-reported outcomes or quality-of-life metrics. Thus, while the LAS achieves its mission of decreasing transplant-related mortality, there is work to be done in engaging transplant candidates and recipients, as well as regulatory agencies, third party payers, and advocacy organizations, to better define important outcomes in this population beyond early survival metrics. Key stakeholders would also contribute to developing strategies for addressing those needs and incorporating patient-centered outcomes into program performance metrics.

These advances and efforts mark an excellent starting point for improving the transplantation process and criteria; however, more work needs to be done to improve access to lung transplantation and post-transplantation outcomes. Currently, the ability to conduct multicenter trials in the Boston area, with the need for identifying funding and overcoming procedural and logistical complications, remains a critical challenge to overcome.

Charge 4c. Improve public awareness and recognition of pulmonary hypertension

[2] More campaign information can be found on the Donate Life website at: https://www.donatelife.net/ and at https://registerme.org/MA/?utm_source=Google&utm_campaign=Organ19&utm_medium=sitelink&utm_term=ad2&utm_content=register

Recommendation 1: Promote Massachusetts based pulmonary hypertension events by engaging multiple mainstream, internet and social media outlets to utilize earned, public service, and paid media.

Recommendation 2: Distribute accurate and publicly available resources to medical-based locations such as primary care providers' offices for placement in waiting rooms and patient exam rooms.

Recommendation 3: Develop and implement a statewide public awareness campaign designed to reach people outside of traditional health care settings.

As pulmonary hypertension is not well known and understood, and as its symptoms can be consistent with other more well-known diseases, an increase in awareness and knowledge of the disease and its symptoms among the general public would be crucial to reducing delays in diagnosis.

PHA and Pulmonary Hypertension Aware or PHAware (an international nonprofit association also based in education, advocacy, and research support) are examples of two organizations that provide a breadth of communication, education, and support resources for patients, family/caregivers, and the general public. Formats include materials such as fact sheets and checklists, blogs, podcasts, livestream questions and answers, an online classroom, a pre-prepared awareness campaign toolkit, pulmonary hypertension specialists and care center databases, and clinical trial registries. Their mechanisms to disseminate information include email mailing lists, websites, Facebook, Twitter, community campaigns and engagement events, fundraising events, and support groups. PHA also has a story bank that could be utilized as personal stories can be powerful, motivating, and a great way of moving pulmonary hypertension into the general public's awareness. November is now Pulmonary Hypertension Awareness Month (announced by Congress in 2018), an optimal time to focus on educational efforts.

The following components are necessary for an effective statewide communication campaign:

- Use of research-based strategies to shape materials and products and to select the channels that deliver them to the intended audience.
- Understanding of concepts, language, and priorities for different cultures and settings.
- Consideration of health literacy, internet access, media exposure, and cultural competency of target populations.
- Development of materials such as brochures, billboards, newspaper articles, television broadcasts, radio commercials, public service announcements, newsletters, pamphlets, videos, digital tools, case studies, and health fairs.

Charge 4d. Improve health care delivery for individuals with a diagnosis of pulmonary hypertension

Recommendation: Explore strategies to improve patient care coordination between primary care physicians and pulmonary hypertension specialists.

Pulmonary hypertension patients are typically managed over time by both primary care and pulmonary hypertension specialists. Some patients are often reluctant to use primary care providers to manage their

health because of the complexity of their disease process. Additionally, some primary care providers lack understanding of pulmonary hypertension and what the essential medical triggers are to then involve the patient's specialist. Therefore, effective and continuous communication and coordination of care between primary care providers and pulmonary hypertension specialists is essential to better address the overall care of patients.

Charge 4e. Improve the early and accurate diagnosis of pulmonary hypertension.

Recommendation: Provide education and training to build the capacity of primary care providers to understand pulmonary hypertension and improve early diagnosis and treatment.

As mentioned in Section II, pulmonary hypertension is a complex and often misunderstood disease. It can be difficult to diagnose, and there can be long delays from initial presentation of symptoms to diagnosis and treatment. Primary care providers must have knowledge of disease symptoms, and diagnostic guidelines and tools to know which tests to order for early and accurate diagnosis of pulmonary hypertension. Patients can then be referred to a pulmonary hypertension specialist who can determine what is causing their disease and develop treatment plans that address their specific group of pulmonary hypertension.

There are a variety of accepted mechanisms that could be utilized:

- Medical education through the inclusion of pulmonary hypertension elements
- Hospital grand rounds to keep providers up-to-date on pulmonary hypertension outside of primary care core practice
- Continuing medical education programs—used for continuous professional development to improve practice standards and patient care—to ensure providers remain current on pulmonary hypertension
    - Programs could be offered through the Pulmonary Hypertension Association, Massachusetts Medical Society, and other professional associations.
    - The provision of continuing medical education credits is a standard practice to provide an incentive as well as to build the number of required credit hours each year for physicians to maintain medical licensure.
- Membership in a professional organization(s) such as PHA to be connected to pulmonary hypertension medical networks and expertise; pulmonary hypertension care centers; *Advances in Pulmonary Hypertension* quarterly medical journal; education and training opportunities through their Early Diagnosis Campaign, conferences, an online university; and resources for patients.

The involvement of pulmonary hypertension patients could be incorporated into one or more of these mechanisms, so that they can speak firsthand about their experiences and provide an enhanced learning opportunity.

As noted earlier, there are professional organizations that provide a variety of educational resources and training opportunities to the provider community (as well as for patients, family/caregivers, and the general public). A teacher or mentor partnership/collaboration could be established with medical educational programs, teaching hospitals, and/or professional associations to leverage the availability of expertise.

Charge 4f. Systematically advance the full spectrum of biomedical research on pulmonary hypertension

See recommendations for Charges 4a and 4b.

References:

- American Transplant Foundation. National Donate Life Month, 2018. Accessed at: https://www.americantransplantfoundation.org/2019/04/01/april-is-national-donate-life-month/

- *American Journal of Transplantation* information about Spain's model https://www.eurekalert.org/pub_releases/2017-01/w-hsa010617.php

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- Samuel, Leah. To solve organ shortage, states consider 'opt-out' organ donation laws. STAT, July 6, 2017. Accessed at: https://www.statnews.com/2017/07/06/opt-solution-organ-shortage/.

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ATTACHMENT A: SUMMARY OF ADVANCES MADE IN RESEARCH ON TREATMENT AND DIAGNOSIS OF PULMONARY HYPERTENSION

In spring 2019, the task force conducted a website search of key organizations, looking for new information regarding research advances in the disease's surveillance, diagnosis, and treatment. This background research informed the April 2019 task force meeting discussion. The following sites were reviewed:

1. Centers for Disease Control and Prevention
2. Pulmonary Hypertension Association
3. Pulmonary Hypertension Association Registry
4. American Heart Association
5. National Heart, Lung, and Blood Institute
6. World Health Organization

The information on these websites had not changed significantly in the past year. A second search on MedlinePlus and Pubmed's sites did not reveal significant changes in the medical community's knowledge of the disease, its diagnosis, and treatment.

The majority of advances made in the field of pulmonary hypertension come from research presented at the World Symposium on Pulmonary Hypertension. Aware of this group, the task force anticipated the release of articles from the last Symposium meeting (held in 2018); the European Respiratory Journal published these 13 articles in January 2019. Of these, two publications discuss the diagnosis and definition of pulmonary hypertension, one describes the importance of patient perspectives, and 10 outline clinical research, treatments, and disease classifications. Please see the list of articles below for more information.

Reviewing the Pulmonary Hypertension Association website led to the discovery of the American College of Chest Physicians' (CHEST) updated guideline on pulmonary arterial hypertension. In March 2019, CHEST convened an expert panel to review and update recommendations pertaining to pulmonary arterial hypertension, which were last updated in 2014. The resulting report includes two new recommendations on combination therapy, statements regarding palliative care, and a treatment algorithm intended to guide physicians through an organized approach to disease management. The panel also conducted an extensive literature search, which indicates that therapeutic options for pulmonary arterial hypertension patients are expanding.

Sources:

European Respiratory Society. "World Symposium on Pulmonary Hypertension." *European Respiratory Journal,* vol. 53, no. 1. January 2019. https://erj.ersjournals.com/content/53/1#Series

Klinger, James R., et. al. "Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report." *Chest,* vol. 155, no. 3 (565–586). March 2019. https://journal.chestnet.org/article/S0012-3692(19)30002-9/fulltext#sec4.2

Articles Published from the 2018 World Symposium on Pulmonary Hypertension

The 13 articles listed below are organized into the following categories: Pulmonary Hypertension Diagnosis and Definition; Patient Perspectives in Pulmonary Hypertension; and Clinical Research, Treatments, and Classifications. Link to all articles: https://erj.ersjournals.com/content/53/1#Series

Pulmonary Hypertension Diagnosis and Definition

Diagnosis of Pulmonary Hypertension
Adaani Frost, David Badesch, J. Simon R. Gibbs, Deepa Gopalan, Dinesh Khanna, Alessandra Manes, Ronald Oudiz, Toru Satoh, Fernando Torres, Adam Torbicki
European Respiratory Journal, 24 January 2019
Abstract: A revised diagnostic algorithm provides guidelines for the diagnosis of patients with suspected pulmonary hypertension, both prior to and following referral to expert centres, and includes recommendations for expedited referral of high-risk or complicated patients and patients with confounding comorbidities. New recommendations for screening high-risk groups are given, and current diagnostic tools and emerging diagnostic technologies are reviewed.

Paediatric Pulmonary Arterial Hypertension: Updates on Definition, Classification, Diagnostics and Management
Erika B. Rosenzweig, Steven H. Abman, Ian Adatia, Maurice Beghetti, Damien Bonnet, Sheila Haworth, D. Dunbar Ivy, Rolf M.F. Berger
European Respiratory Journal, 24 January 2019
Abstract: Paediatric pulmonary arterial hypertension (PAH) shares common features of adult disease, but is associated with several additional disorders and challenges that require unique approaches. This article discusses recent advances, ongoing challenges and distinct approaches for the care of children with PAH, as presented by the Paediatric Task Force of the 6th World Symposium on Pulmonary Hypertension. We provide updates of the current definition, epidemiology, classification, diagnostics and treatment of paediatric PAH, and identify critical knowledge gaps. Several features of paediatric PAH including the prominence of neonatal PAH, especially in pre-term infants with developmental lung diseases, and novel genetic causes of paediatric PAH are highlighted. The use of cardiac catheterisation as a diagnostic modality and haemodynamic definitions of PAH, including acute vasoreactivity, are addressed. Updates are provided on issues related to utility of the previous classification system to reflect paediatric-specific aetiologies and approaches to medical and interventional management of PAH, including the Potts shunt. Although a lack of clinical trial data for the use of PAH-targeted therapy persists, emerging data are improving the identification of appropriate targets for goal-oriented therapy in children. Such data will likely improve future clinical trial design to enhance outcomes in paediatric PAH.

Patient Perspectives in Pulmonary Hypertension

The Importance of Patient Perspectives in Pulmonary Hypertension
Michael D. McGoon, Pisana Ferrari, Iain Armstrong, Migdalia Denis, Luke S. Howard, Gabi Lowe, Sanjay Mehta, Noriko Murakami, Brad A. Wong
European Respiratory Journal, 24 January 2019

Abstract: The assessment of objective measurement of cardiopulmonary status has helped us achieve better clinical outcomes for patients and develop new therapies through to the point of market access; however, patient surveys indicate that more can be done to improve holistic care and patient engagement. In this multidisciplinary review, we examine how clinical teams can acknowledge and embrace the individual patient's perspective, and thus improve the care for individual patients suffering from pulmonary hypertension by cultivating the importance and relevance of health-related quality of life in direct clinical care. At the individual level, patients should be provided with access to accredited specialist centres which provide a multidisciplinary approach where there is a culture focused on narrative medicine, quality of life, shared decision making and timely access to palliative care, and where there is participation in education. On a larger scale, we call for the development, expansion and promotion of patient associations to support patients and carers, lobby for access to best care and treatments, and provide input into the development of clinical trials and registries, focusing on the patients' perspective.

Clinical Research, Treatments, and Classifications

Pathology and Pathobiology of Pulmonary Hypertension: State of the Art and Research Perspectives

Marc Humbert, Christophe Guignabert, Sébastien Bonnet, Peter Dorfmüller, James R. Klinger, Mark R. Nicolls, Andrea J. Olschewski, Soni S. Pullamsetti, Ralph T. Schermuly, Kurt R. Stenmark, Marlene Rabinovitch

European Respiratory Journal, 24 January 2019

Abstract: Clinical and translational research has played a major role in advancing our understanding of pulmonary hypertension (PH), including pulmonary arterial hypertension and other forms of PH with severe vascular remodelling (e.g. chronic thromboembolic PH and pulmonary veno-occlusive disease). However, PH remains an incurable condition with a high mortality rate, underscoring the need for a better transfer of novel scientific knowledge into healthcare interventions. Herein, we review recent findings in pathology (with the questioning of the strict morphological categorisation of various forms of PH into pre- or post-capillary involvement of pulmonary vessels) and cellular mechanisms contributing to the onset and progression of pulmonary vascular remodelling associated with various forms of PH. We also discuss ways to improve management and to support and optimise drug development in this research field.

Genetics and Genomics of Pulmonary Arterial Hypertension

Nicholas W. Morrell, Micheala A. Aldred, Wendy K. Chung, C. Gregory Elliott, William C. Nichols, Florent Soubrier, Richard C. Trembath, James E. Loyd

European Respiratory Journal, 24 January 2019

Abstract: Since 2000 there have been major advances in our understanding of the genetic and genomics of pulmonary arterial hypertension (PAH), although there remains much to discover. Based on existing knowledge, around 25–30% of patients diagnosed with idiopathic PAH have *an underlying Mendelian genetic cause for their condition and should be classified as heritable PAH (HPAH). Here, we summarise the known genetic and genomic drivers of PAH, the insights these provide into pathobiology, and the opportunities afforded for development of novel therapeutic approaches. In addition, factors determining the incomplete penetrance observed in HPAH are discussed. The currently available approaches to genetic testing and counselling, and the impact of a genetic diagnosis on clinical management of the patient with PAH, are presented. Advances in DNA sequencing technology are rapidly expanding our ability to undertake*

genomic studies at scale in large cohorts. In the future, such studies will provide a more complete picture of the genetic contribution to PAH and, potentially, a molecular classification of this disease.

Pathophysiology of the Right Ventricle and of the Pulmonary Circulation in Pulmonary Hypertension: an Update

Anton Vonk Noordegraaf, Kelly Marie Chin, François Haddad, Paul M. Hassoun, Anna R. Hemnes, Susan Roberta Hopkins, Steven Mark Kawut, David Langleben, Joost Lumens, Robert Naeije

European Respiratory Journal, 24 January 2019

Abstract: The function of the right ventricle determines the fate of patients with pulmonary hypertension. Since right heart failure is the consequence of increased afterload, a full physiological description of the cardiopulmonary unit consisting of both the right ventricle and pulmonary vascular system is required to interpret clinical data correctly. Here, we provide such a description of the unit and its components, including the functional interactions between the right ventricle and its load. This physiological description is used to provide a framework for the interpretation of right heart catheterisation data as well as imaging data of the right ventricle obtained by echocardiography or magnetic resonance imaging. Finally, an update is provided on the latest insights in the pathobiology of right ventricular failure, including key pathways of molecular adaptation of the pressure overloaded right ventricle. Based on these outcomes, future directions for research are proposed.

Haemodynamic Definitions and Updated Clinical Classification of Pulmonary Hypertension

Gérald Simonneau, David Montani, David S. Celermajer, Christopher P. Denton, Michael A. Gatzoulis, Michael Krowka, Paul G. Williams, Rogerio Souza

European Respiratory Journal, 24 January 2019

Abstract: Since the 1st World Symposium on Pulmonary Hypertension (WSPH) in 1973, pulmonary hypertension (PH) has been arbitrarily defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, measured by right heart catheterisation. Recent data from normal subjects has shown that normal mPAP was 14.0±3.3 mmHg. Two standard deviations above this mean value would suggest mPAP >20 mmHg as above the upper limit of normal (above the 97.5th percentile). This definition is no longer arbitrary, but based on a scientific approach. However, this abnormal elevation of mPAP is not sufficient to define pulmonary vascular disease as it can be due to an increase in cardiac output or pulmonary arterial wedge pressure. Thus, this 6th WSPH Task Force proposes to include pulmonary vascular resistance ≥3 Wood Units in the definition of all forms of pre-capillary PH associated with mPAP >20 mmHg. Prospective trials are required to determine whether this PH population might benefit from specific management.
Regarding clinical classification, the main Task Force changes were the inclusion in group 1 of a subgroup "pulmonary arterial hypertension (PAH) long-term responders to calcium channel blockers", due to the specific prognostic and management of these patients, and a subgroup "PAH with overt features of venous/capillaries (pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis) involvement", due to evidence suggesting a continuum between arterial, capillary and vein involvement in PAH.

Risk Stratification and Medical Therapy of Pulmonary Arterial Hypertension

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Abstract: Pulmonary arterial hypertension (PAH) remains a severe clinical condition despite the availability over the past 15 years of multiple drugs interfering with the endothelin, nitric oxide and prostacyclin pathways. The recent progress observed in medical therapy of PAH is not, therefore, related to the discovery of new pathways, but to the development of new strategies for combination therapy and on escalation of treatments based on systematic assessment of clinical response. The current treatment strategy is based on the severity of the newly diagnosed PAH patient as assessed by a multiparametric risk stratification approach. Clinical, exercise, right ventricular function and haemodynamic parameters are combined to define a low-, intermediate- or high-risk status according to the expected 1-year mortality. The current treatment algorithm provides the most appropriate initial strategy, including monotherapy, or double or triple combination therapy. Further treatment escalation is required in case low-risk status is not achieved in planned follow-up assessments. Lung transplantation may be required in most advanced cases on maximal medical therapy.

Intensive Care, Right Ventricular Support and Lung Transplantation in Patients with Pulmonary Hypertension

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European Respiratory Journal, 24 January 2019

Abstract: Intensive care of patients with pulmonary hypertension (PH) and right-sided heart failure includes treatment of factors causing or contributing to heart failure, careful fluid management, and strategies to reduce ventricular afterload and improve cardiac function. Extracorporeal membrane oxygenation (ECMO) should be considered in distinct situations, especially in candidates for lung transplantation (bridge to transplant) or, occasionally, in patients with a reversible cause of right-sided heart failure (bridge to recovery). ECMO should not be used in patients with end-stage disease without a realistic chance for recovery or for transplantation. For patients with refractory disease, lung transplantation remains an important treatment option. Patients should be referred to a transplant centre when they remain in an intermediate- or high-risk category despite receiving optimised pulmonary arterial hypertension therapy. Meticulous peri-operative management including the intra-operative and post-operative use of ECMO effectively prevents graft failure. In experienced centres, the 1-year survival rates after lung transplantation for PH now exceed 90%.

Clinical Trial Design and New Therapies for Pulmonary Arterial Hypertension

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Abstract: Until 20 years ago the treatment of pulmonary arterial hypertension (PAH) was based on case reports and small series, and was largely ineffectual. As a deeper understanding of the pathogenesis and pathophysiology of PAH evolved over the subsequent two decades, coupled with epidemiological studies defining the clinical and demographic characteristics of the condition, a renewed interest in treatment development emerged through collaborations between international *experts, industry and regulatory agencies. These efforts led to the performance of robust, high-quality clinical trials of novel therapies that targeted putative pathogenic pathways, leading to the approval of more than 10 novel therapies that have beneficially impacted both the quality and duration of life. However, our understanding of PAH remains incomplete and there is no cure. Accordingly, efforts are now focused on identifying novel pathogenic pathways that may be targeted, and applying more rigorous clinical trial designs to better define the efficacy*

of these new potential treatments and their role in the management scheme. This article, prepared by a Task Force comprised of expert clinicians, trialists and regulators, summarises the current state of the art, and provides insight into the opportunities and challenges for identifying and assessing the efficacy and safety of new treatments for this challenging condition.

Pulmonary hypertension due to left heart disease

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European Respiratory Journal, 24 January 2019

Abstract: Pulmonary hypertension (PH) is frequent in left heart disease (LHD), as a consequence of the underlying condition. Significant advances have occurred over the past 5 years since the 5th World Symposium on Pulmonary Hypertension in 2013, leading to a better understanding of PH-LHD, challenges and gaps in evidence. PH in heart failure with preserved ejection fraction represents the most complex situation, as it may be misdiagnosed with group 1 PH. Based on the latest evidence, we propose a new haemodynamic definition for PH due to LHD and a three-step pragmatic approach to differential diagnosis. This includes the identification of a specific "left heart" phenotype and a non-invasive probability of PH-LHD. Invasive confirmation of PH-LHD is based on the accurate measurement of pulmonary arterial wedge pressure and, in patients with high probability, provocative testing to clarify the diagnosis. Finally, recent clinical trials did not demonstrate a benefit in treating PH due to LHD with pulmonary arterial hypertension-approved therapies.

Pulmonary Hypertension in Chronic Lung Disease and Hypoxia

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Abstract: Pulmonary hypertension (PH) frequently complicates the course of patients with various forms of chronic lung disease (CLD). CLD-associated PH (CLD-PH) is invariably associated with reduced functional ability, impaired quality of life, greater oxygen requirements and an increased risk of mortality. The aetiology of CLD-PH is complex and multifactorial, with differences in the pathogenic sequelae between the diverse forms of CLD. Haemodynamic evaluation of PH severity should be contextualised within the extent of the underlying lung disease, which is best gauged through a combination of physiological and imaging assessment. Who, when, if and how to screen for PH will be addressed in this article, as will the current state of knowledge with regard to the role of treatment with pulmonary vasoactive agents. Although such therapy cannot be endorsed given the current state of findings, future studies in this area are strongly encouraged.

Chronic Thromboembolic Pulmonary Hypertension

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Abstract: Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of pulmonary embolism and a major cause of chronic PH leading to right heart failure and death. Lung ventilation/perfusion scintigraphy is the screening test of choice; a normal scan rules out CTEPH. In the case of an abnormal perfusion scan, a high-quality pulmonary angiogram is necessary to confirm and define the pulmonary vascular involvement and prior to making a treatment decision. PH is confirmed with right heart

catheterisation, which is also necessary for treatment determination. In addition to chronic anticoagulation therapy, each patient with CTEPH should receive treatment assessment starting with evaluation for pulmonary endarterectomy, which is the guideline recommended treatment. For technically inoperable cases, PH-targeted medical therapy is recommended (currently riociguat based on the CHEST studies), and balloon pulmonary angioplasty should be considered at a centre experienced with this challenging but potentially effective and complementary intervention.