Personalized Medicine for Pulmonary Hypertension: The Future Management of Pulmonary Hypertension Requires a New Taxonomy

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INTRODUCTION

Pulmonary hypertension (PH), whether defined by a resting mean pulmonary artery pressure (mPAP) greater than 20 mm Hg or greater than or equal to 25 mm Hg, is classified into 5 major groups by international consensus (Box 1). The classification, first considered in 1973 and revisited at regular intervals since, seeks to include all clinical conditions associated with the development or progression of PH. Patients are assigned to a major group according to whether their PH is judged to be precapillary or postcapillary and the nature of any comorbidities.

Precapillary PH is distributed over Groups 1, 3, 4 and 5 while post-capillary PH is found in Groups 2 and 5. Group 1, labeled pulmonary arterial hypertension (PAH), hosts idiopathic (IPAH), heritable (HPAH), and drug-induced PH, which are diagnoses of exclusion of coexisting diseases, alongside PH caused by congenital heart disease, PH associated with connective tissue lung disease, and porto-pulmonary PH. Group 3 includes lung disease, including idiopathic pulmonary fibrosis, obstructive sleep apnea and chronic obstructive pulmonary disease, and hypoxia-induced PH. Group 4 is PH caused by chronic thromboembolic disease. Left-sided heart failure from whatever cause is placed in Group 2. Group 5 includes PH from a miscellaneous collection of comorbidities.

This classification is used to develop and assign treatments. There has been some success. Drugs that improve patient symptoms have been licensed for Group 1 and Group 4. Group 1 and Group 4 represent rare conditions with unmet clinical needs and an accelerated route to market. But progress with the development of treatments for PH in Group 2 and Group 3, the most common presentations of PH, has been disappointing. Mortality in these groups remains high, with both elevated pulmonary artery pressure and right
ventricular dysfunction representing independent predictors of death. Even in Group 1, progress with developing effective therapies is qualified by a lack of impact on disease progression; these drugs, particularly in combination, may slow disease progression but do not arrest or reverse it. This is evident in survival statistics, which show that 5-year mortality is near 50%.

Fortunately, pulmonary vascular disease remains an active area for drug discovery. There is no shortage of potential therapeutic targets, for both new chemical entities and repurposed drugs. To improve success, however, future treatments for PH need to be focused more acutely on the patient as an individual, rather than the patient as part of a group, and this requires a new taxonomy of pulmonary vascular disease.

FIRST, THE PROBLEM WITH AVERAGES

It is widely recognized that patients vary in their response to drugs. This is evident in all studies evaluating treatments for PH. It can be easily overlooked when the data are presented as the mean change in each study group, even when shown with confidence intervals. For example, in a Phase 3 study with imatinib (IMPRES), which investigated the effects of imatinib in patients with Group 1 PAH, the mean placebo-corrected change in 6-minute walk distance (6MWD) after 24 weeks was 32 m (95% confidence interval, 12–52 m; \( P = .002 \)). When the absolute change in 6MWD is plotted as a distribution, the range of responses becomes stark (Fig. 1) and difficult to ignore. The fact that more patients improved with active treatment is still evident, but it becomes clear that some patients did not show a beneficial response as judged by the change in their 6MWD.

Various factors, both extrinsic and intrinsic, may influence the outcome measurement. Some, such as concomitant medication, comorbidity, and the genetics of drug transport and metabolism, may

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**Box 1**
Clinical classification of pulmonary hypertension

**Group 1: PAH**
Subgroups
- Idiopathic PAH
- Heritable PAH
- Drug- and toxin-induced PAH
- PAH associated with:
  - Connective tissue disease
  - HIV infection
  - Portal hypertension
  - Congenital heart disease
  - Schistosomiasis
- PAH long-term responders to calcium channel blockers
- PAH with overt features of venous/capillaries (pulmonary venous occlusive disease/pulmonary capillary hemangiomatisis) involvement
- Persistent PH of the newborn syndrome

**Group 2: PH caused by left heart disease**
Subgroups
- PH caused by heart failure with preserved left ventricular ejection fraction (LVEF)
- PH due to heart failure with reduced LVEF
- Valvular heart disease
- Congenital/acquired cardiovascular conditions leading to postcapillary PH

**Group 3: PH caused by lung diseases and/or hypoxia**
Subgroups
- Obstructive lung disease
- Restrictive lung disease
- Other lung disease with mixed restrictive/obstructive pattern
- Hypoxia without lung disease
- Developmental lung disorders

**Group 4: PH caused by pulmonary artery obstructions**
Subgroups
- Chronic thromboembolic PH
- Other pulmonary artery obstructions

**Group 5: PH with unclear and/or multifactorial mechanisms**
Subgroups
- Hematological disorders

Abbreviations: PCH, pulmonary capillary hemangiomatisis; PVOD, pulmonary veno-occlusive disease.

affect the pharmacokinetics of the study medication. Others, such as age, comorbidity, and heritable factors, can affect the pharmacodynamic response.

Prior consideration is given to these in the design of clinical trial protocols, with the aim of minimizing the noise to improve detection of the signal, but pragmatic factors intervene. A consideration of the process around designing a study for Group 1 PAH illustrates this. Because the aim is to find a treatment for pulmonary vascular disease, these studies start out targeting patients with idiopathic, heritable, and drug-induced PAH to reduce the influence of comorbidity. Boundaries are set for age, baseline walk distance, hemodynamics, and licensed therapies. In deciding the inclusion and exclusion criteria, there will be a discussion around whether to enroll patients with connective tissue disease and what constitutes significant parenchymal lung disease. Once the study is started, time pressures on recruitment from a rare patient population mean that trial protocols extend inclusion criteria (or patients are recruited that an adjudication panel might question), and the final study population is not so pure. In the end, patients are recruited from additional subgroups within Group 1, and so trials finish with a cohort of patients with mixed underlying pathology.  

If the mean response to the study drug is judged to be clinically beneficial in a pivotal trial, the study drug may be licensed for all of Group 1 PAH. The inclusion of small but representative patients from other PAH subgroups in Group 1 is used to justify this. A trivial but enlightening example of the folly of this approach is to apply it to waist size. No one would take the average waist size of a cohort to design a pair of trousers to fit all. Yet this is what is done for drugs for PAH, driven admittedly by the desire to offer a treatment for a desperate medical condition.

At best, this practice may dilute any signal of efficacy. At worst, the signal may be lost altogether in the average response, and potential therapies may be discarded. A post hoc responder analysis is often used in a successful study to explore whether benefit is observed across all patient groups or, in a less successful trial, to determine whether there is a subgroup that showed some benefit. Unfortunately, the granularity of information available from clinical trials to make this meaningful is poor. Analysts have to rely on a limited clinical vocabulary and range of investigations.

**THE LIMITATIONS OF THE CURRENT CLINICAL CLASSIFICATION**

The clinical classification of PH was never intended as a guide to drug development. It is understandable that it has been adopted as such, in the absence of anything else, but it was first proposed with the aim of collating the clinical and histologic characteristics of PH. Importantly, it is not based on a deep comprehension of pulmonary vascular disease and plausible drug targets. Iterative revisions have resulted in a few new subgroups or reassigning a patient subgroup to a different major group, but the major categories have remained the same. Simple inspection shows heterogeneity and ambiguity within and between...
the major groups, a statement to a limited understanding of underlying pathology. In clinical practice, patients can move from one subgroup to another or even a different major group during the course of their illness.

The problem starts with the defining investigation of PH. A key measurement in the diagnostic workup of a patient is the pulmonary artery wedge pressure (PAWP); it influences the group to which a PH patient is assigned. Greater than 15 mm Hg is considered to be raised and indicates a high left-sided filling pressure caused by significant left heart disease; the patient is placed in Group 2 (or in a few cases, Group 5). This is not always an easy measurement to make with confidence, and yet a difference of 1 mm Hg can define a patient’s diagnostic category and his or her suitability for licensed targeted treatments.

A further complication is that 12% to 38% of patients with PH and a raised PAWP have evidence of a precapillary component to their PH phenotype, based on a diastolic pressure gradient of at least 7 mm Hg or pulmonary vascular resistance (PVR) greater than 3 Wood units. The European Society of Cardiology and European Respiratory Society guidelines recognize these patients as having combined precapillary and postcapillary PH. With an aging population, the number of patients in this category is likely to grow.

The changing demographics of patients also adds complexity to the diagnosis of IPAH. IPAH is now more frequently diagnosed in older (>55 years) patients, but many in the older age group have cardiovascular risk factors (eg, coronary artery disease, systemic hypertension, hyperlipidemia, or diabetes) that predispose to left heart disease. IPAH patients with at least 3 cardiovascular risk factors have been labeled atypical IPAH. The risk profiles and demographic characteristics of patients with atypical IPAH resemble those of PH with heart failure, particularly heart failure with preserved ejection fraction (HFpEF); many of these patients might be regarded as having combined precapillary and postcapillary PH. It has been proposed that typical IPAH, atypical IPAH, and HFpEF might form a disease continuum.

This has implications for clinical trials. Data from patient registries and from clinical trials indicate that patients with PAH and additional cardiovascular risk factors are less responsive to targeted PAH treatments and show higher discontinuation rates. In brief, a spectrum of structural changes affecting arterioles through to venules is seen in PH that underscores the difficulty of using hemodynamic measurements to separate disease entities.

INSIGHTS FROM GENETICS

An inevitable conclusion from this discussion is that PH is a convergent phenotype, the end manifestation of several pathologic drivers, and that clinical descriptors are blunt tools for dissecting the late-stage clinical presentation of PH. The development of effective new treatments depends on a better understanding of the pathologic mechanisms operating at a more individual level. Genetics is a good place to start.

Progress with understanding the genetic architecture of PH is most advanced in heritable and
idiopathic PAH. Pathogenic mutations in \textit{BMPR2}, which encodes bone morphogenetic protein receptor type-2 (BMPR-2), segregate with PAH in families with a history of the condition.\textsuperscript{21,22} These mutations predict loss of function. BMPR-2 is a member of the transforming growth factor-β (TGF-β) signaling pathway, and the working hypothesis is that reduced BMPR-2 activity creates an imbalance in bone morphogenetic protein (BMP)–TGF-β, in favor of TGF-β. Rare deleterious variants are now well documented in other genes in this pathway in PAH patients, emphasizing its significance, notably \textit{GDF-2}, \textit{ACVRL1}, \textit{ENG}, and \textit{SMAD8}.\textsuperscript{23} Nonetheless, there is a growing list of genes associated with PAH out with those with a direct impact on BMP-TGF-β signaling, including \textit{KCNK3}, \textit{TBX4}, \textit{SOX17}, \textit{ATP13A3}, \textit{AQPI}, \textit{ABCC8}, and \textit{KDR}.\textsuperscript{23–25} These studies reveal the genetic diversity underlying a clinical diagnosis of PAH.

The obvious question is, “Does this genetic diversity translate into recognizable clinical
phenotypes? This might be demanding, even for rare mutations, which tend to be associated with a larger effect than common variants. Apart from evidence that PAH patients with BMPR2 mutations have a worse prognosis than patients without documented mutations in this gene, the data are few. But the power of genetics to dissect the PH phenotype and inform clinical management is illustrated by EIF2AK4, a gene associated with pulmonary venous occlusive disease (PVOD). In a UK study of 880 patients with IPAH, HPAH, or drug-induced PAH, 9 patients carried biallelic EIF2AK4 mutations, despite a clinical diagnosis of IPAH made in an expert center. Further investigation of clinical records showed that these patients were younger, had a reduced transfer coefficient for carbon monoxide (Kco), and more interlobular septal thickening and mediastinal lymphadenopathy on computed tomography of the chest compared with patients with PAH without EIF2AK4 mutations. Radiological assessment alone could not accurately identify the biallelic EIF2AK4 mutation carriers. Patients with PVOD may not do well if given treatments currently licensed for PAH. The lesson is that young patients with a clinical diagnosis of PAH and low Kco should be tested for EIF2AK4 mutations.

These genetic insights not only mandate care in patient selection for clinical trials, they also inform drug development. Reviewing the high attrition rate in this space, it is keenly noted that selecting genetically validated drug targets can increase success rates. In consequence, a genetic link between a druggable target and a disease should prioritize that target for further investigation. In that context, targeting BMP-TGF-β signaling deserves priority. The most clinically advanced strategy involves using a fusion protein (Sotatercept) consisting of the extracellular domain of activin receptor IIa (ActRIIa) attached to the Fc portion of human immunoglobulin G1 (IgG1) to sequester TGF-β superfamily ligands, such as activin A and B and growth differentiation factor (GDF)-11, thereby suppressing TGF-β signaling and rebalancing deficient BMPR-2 signaling (ClinicalTrials.gov Identifier: NCT03496207). Early reports from a Phase 2 study are encouraging, and the detail around the data is anticipated with interest. Another approach under early clinical evaluation is directed at improving post-BMPR-2 signaling with tacrolimus. Administering BMP9, a ligand for BMPR-2, is an option in preclinical development, based on the association between GDF2 mutations and PAH.

Whether these treatments should or could be targeted more accurately is yet unknown, but detailed knowledge of the 300-plus mutations identified in BMPR2 suggest more selective therapies. Aside from exogenous BMPR2 gene delivery, still some time away in terms of clinical investigation, there are more immediate options for novel or repurposed drugs. Around 70% of BMPR2 mutations are nonsense (frame-shift deletions and insertions) mutations. Aminoglycoside antibiotics and drugs such as ataluren permit read-through of premature stop codons and the translation of full-length protein. Around 30% of mutations are missense mutations with single amino acid substitutions, disrupting protein folding and trafficking to the cell surface; chemical chaperones, such as sodium phenyl-butyrte, may rescue BMPR-2 trafficking, while hydroxychloroquine and chloroquine may have a beneficial effect by inhibiting autophagic degradation of BMPR-2. Studies are in setup to examine whether therapies directed at specific BMPR2 mutations offer therapeutic benefit in PAH, taking personalized medicine to the point of a private medicine.

How far can this be taken? It remains to be established whether other genetically defined targets and their downstream pathways (ie, outside of BMP-TGF-β signaling) are druggable and might permit more precise targeting. Furthermore, the list of genes currently identified accounts for only 25% to 30% of IPAH patients. Additional rare variants that influence thrombosis, inflammation, right ventricular (RV) function and other relevant pathologies may emerge from large-scale international efforts underway, but for most patients with PAH, and certainly PH, there will not be a single major genetic determinant of their phenotype. Common genetic variants, such as those found to influence risk of PAH, have a smaller effect on phenotype. There is interest in their collective value to produce polygenic risk scores. Individually, common variants can provide instruments for Mendelian randomization analysis to define mechanistic pathways and inform druggable targets. But the idea that complex cardiovascular phenotypes, such as PH, can be reduced to a simple genotype-phenotype relationship has been rightfully challenged.

BIG DATA TO THE RESCUE

It has been proposed that complex cardiovascular phenotypes are the clinical manifestation of an interaction of subphenotypes or endo-phenotypes. And that these can be resolved by big data.

The importance of accurate phenotyping to the interpretation of genetic data has long been recognized. The value of deep phenotyping, collecting as much information about a patient as possible,
has taken on greater significance with the opportunity to use machine learning and network analysis to find clusters that relay clinical information. There are emerging examples of the potential value of this approach.

In a cohort of patients with a clinical diagnosis of HFrEF, a suite of statistical learning algorithms used to analyze phenotype data (67 continuous variables) classified participants into 3 distinct groups that differed markedly in clinical characteristics, cardiac structure and function, invasive hemodynamics, and outcomes.\textsuperscript{36} Using data from invasive cardiopulmonary exercise testing (iCPET), network analysis of clinical parameters from 738 patients enabled the development of a novel 10-variable model that defined 4 exercise groups.\textsuperscript{37} The patient groups were characterized by exercise profiles drawn from pulmonary function, exercise hemodynamics, and metabolic data and defined differences in rates of hard clinical end points, expanding the range of useful clinical variables beyond peak VO\textsubscript{2} that predict hospitalization in patients with exercise intolerance.

Cardiac imaging readily provides high-dimensional data that can be used to better capture the nonlinear motion dynamics of the beating heart. These data can be mined for phenotypes beyond crude measures of global contraction that are only moderately reproducible and insensitive to the underlying disturbances of cardiovascular physiology. In a study of 302 patients with PH, image sequences of the heart acquired using cardiac magnetic resonance imaging (MRI) were used to create time-resolved 3-dimensional segmentations using a fully convolutional network trained on anatomic shape priors.\textsuperscript{38} The resulting model was used for survival predictions and outperformed a conventional model based on manually derived volumetric measures.

Advances in technology increase the prospects of collecting more detailed clinical phenotypic information while patients are engaged in activities of daily living. Experience from implanted devices and wearable sensors that permit remote monitoring of electrocardiogram (ECG), blood pressure, oxygen saturation, mobility, and even environment exposure is racing ahead.\textsuperscript{39,40} Integrated with electronic patient records, the depth and volume of data will provide a detailed database to identify important phenotypes associated with response to drugs that will inevitably cut across current clinical boundaries.

Add to this a wealth of ‘omic’ data from noninvasive sampling and cataloging the proteome, transcriptome, metabolome, and microbiome.\textsuperscript{41–44} It is now possible to measure thousands of analytes in a small aliquot of plasma or serum. High-throughput platforms for measuring up to 5000 proteins and hundreds of identifiable metabolites (and many thousand unannotated more) and microRNAs in the same sample offer a window on the molecular choreography of PH.

It is still early days, with most ‘omic’ data from cross-sectional studies comparing PAH, and indeed, more specifically, IPAH and HPAH, with healthy controls. The main aim of these studies has been to identify molecular signatures of disease that might inform prognosis, with some success. Over 1000 proteins have been measured in the plasma proteome of patients with IPAH and HPAH, identifying several that distinguish these patients from healthy controls and around 40 that relate to survival.\textsuperscript{41} The transcriptome of circulating white cells and the plasma metabolome can also discriminate IPAH and HPAH from health and categorize patients according to risk.\textsuperscript{42,43}

Applied to patients within a larger PH group (as opposed to a clinically defined subgroup) or across currently defined PH groups should bring larger rewards. A panel of 48 circulating cytokines, chemokines, and growth factors has been shown to distinguish immune phenotypes in a population of patients drawn from Group 1 PAH.\textsuperscript{45} Unsupervised machine learning (consensus clustering) classified patients into 4 proteomic immune clusters, without guidance from clinical features. The identified clusters were associated with distinctive clinical risk profiles providing information that was not contained in the clinical descriptions of these patients.

These clusters define inflammation endophenotypes. The availability of big data for describing PH sets the scene for describing further endophenotypes, such as thrombosis, fibrosis, cell proliferation, and autophagy. PH might then be regarded as an assembly of these different endophenotypes.\textsuperscript{35} Understanding how these are perturbed in each patient who presents with a raised mPAP (or indeed, with breathlessness) offers a more granular view of his or her underlying pathology. This, in turn, can be used to guide targeted intervention(s) to repair the condition. Delivering this requires adopting a more extensive toolset for investigating patients and a different approach to treating them.

**TOWARD MECHANISM-BASED THERAPEUTICS**

Much has been made of the similarities between PH and cancer, in particular dysregulated cell proliferation and resistance to apoptosis, to the extent that some drugs developed for malignancies are under investigation for PAH.\textsuperscript{56} Oncology has
begun a transition in treatment strategy toward tumor-agnostic therapies, specifically, the use of drugs based on the genetic and molecular features of the cancer in question without regard to type or primary location.\textsuperscript{47} To move to that scenario in PH will require the depth of molecular knowledge about the PH of each patient that oncology currently enjoys.

Oncology has the advantage of tissue biopsies, permitting sequencing for somatic and germline mutations. PH will need to rely more on liquid biopsies, the composition of circulating molecules that report on health. At present, multiplex assays, such as a panel of proteins, are available that improve on single-protein assays (eg, NT-proBNP) and clinical risk scores for defining risk or prognosis.\textsuperscript{41} Building on this, combinations of circulating factors (ie, molecular signatures) could be used to define druggable pathologic pathways. For example, further network analysis of a proteome dataset from patients with clinically defined PAH has unmasked increased activity of the complement alternative pathway in some patients.\textsuperscript{41,48} A protein cluster was identified that distinguished patients with poor survival, raising interest in trialing intervention with a complement inhibitor (eg, a complement C5a inhibitor) in this group in a biomarker-driven study design. The extent to which the complement alternative pathway is disturbed in other presentations of PH merits investigation.

**THE FUTURE OF PULMONARY HYPERTENSION TREATMENT**

PH is a global unmet clinical need. It progresses silently and presents late as a convergent phenotype. Dividing PH into broad overlapping clinical categories inhibits rather than assists the development of new treatments. The early use of dual therapy and even triple therapy in the management plan for PAH has benefited patients, but it is a desperate response to a deeper problem.

The current licensed treatments have been developed on an empiric basis, rather than on an in-depth understanding of the underlying pathology. Identifying a therapeutic signal and the patients who may benefit most can be lost in the noise. Without change, the next generation of treatments will be constrained by the same limited vocabulary for categorizing a complex phenotype. The ability to deep-phenotype patients at both the clinical and molecular level and integrate with genetic information opens the door to revisiting how one views and manages this condition (Fig. 3). It will require and drive a new taxonomy of PH, one that reduces the reliance on traditional diagnostic criteria alone and incorporates scientific advances in molecular and genetic medicine and innovations in clinical phenotyping, such as advanced imaging and remote sensors.

A major step in this direction has been taken with the National Heart, Lung, and Blood Institute initiative PVDOMICS (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics) study\textsuperscript{49} (Clinicaltrials.gov NCT02980887). The aim of PVDOMICS is to update the classification of pulmonary vascular disease using a combination of deep clinical phenotyping and ‘omic’ techniques. It is important to note that ‘omic’ data are not alternatives to clinical data. Indeed, the project is explicit in requiring in-depth clinical phenotyping using standard operating protocols. The data will be subjected to unbiased network analyses and machine learning to cluster patients according to shared features and identify the molecular basis of these clusters. The expectation is that this will generate new

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**Fig. 3.** Personalized medicine based on consensus clustering of multidimensional data and mechanism-based drug treatment.
pulmonary vascular disease ontologies, highlight relevant druggable pathways, and enable targeted mechanism-based treatments.

This is no small task. It will require validation in a separate data set. It will impact on how clinical trials are performed and drugs are licensed. It will need the combined efforts of all interested in improving the management of patients with PH.

REFERENCES


