Conference Paper

Pulmonary Circulation

What's new in pulmonary hypertension clinical research: lessons from the best abstracts at the 2020 American Thoracic Society International Conference

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Abstract

In this conference paper, we review the 2020 American Thoracic Society International Conference session titled, "What's New in Pulmonary Hypertension Clinical Research: Lessons from the Best Abstracts". This virtual mini-symposium took place on 21 October 2020, in lieu of the annual in-person ATS International Conference which was cancelled due to the COVID-19 pandemic. Seven clinical research abstracts were selected for presentation in the session, which encompassed five major themes: (1) standardizing diagnosis and management of pulmonary hypertension, (2) improving risk assessment in pulmonary arterial hypertension, (3) evaluating biomarkers of disease activity, (4) understanding metabolic dysregulation across the spectrum of pulmonary hypertension, and (5) advancing knowledge in chronic thromboembolic pulmonary hypertension. Focusing on these five thematic contexts, we review the current state of knowledge, summarize presented research abstracts, appraise their significance and limitations, and then discuss relevant future directions in pulmonary hypertension clinical research.

Keywords

pulmonary hypertension, clinical studies, risk stratification and biomarkers, metabolism, pulmonary embolism

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The American Thoracic Society (ATS) International Conference was set for 15–20 May 2020, but unfortunately had to be cancelled due to the COVID-19 pandemic and unprecedented public health crisis. The meeting typically brings together worldwide experts to present and discuss state-of-the-art research in pulmonary and critical care medicine. This year's planned agenda was no different, with several highly anticipated thematic poster sessions, poster discussions, and mini-symposia on the latest research. To highlight the highest impact work submitted for presentation, the ATS Pulmonary Circulation Assembly organized two mini-symposia that were conducted virtually in the Fall of 2020. This review will focus on the virtual session titled "What's New in Clinical Research in Pulmonary Hypertension (PH): Lessons from the Best Abstracts", which took place on 21 October 2020. A second virtual mini-symposium that featured basic science studies is highlighted by a companion review article titled "Recent Advancements in Pulmonary Arterial Hypertension and Right Heart Failure Research: Overview of Selected Abstracts from ATS 2020".

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The PH clinical research mini-symposium was attended by early-stage investigators, senior scientists, and clinicians from across the global pulmonary vascular disease community. This well-received session highlighted seven research abstracts, with one investigator from each study presenting their data. Drs. Corey Ventetuolo (Brown University, Providence, RI), Harm Bogaard (Vrije Universiteit Medical Center, Amsterdam, Netherlands), and Sebastian Bonnet (Université Laval, Quebec, Canada) moderated interactive question and answer discussions after each presentation. Five major research themes emerged: standardizing diagnosis and management of PH, improving risk assessment in pulmonary arterial hypertension (PAH), evaluating biomarkers of disease activity, understanding metabolic dysregulation across the spectrum of PH, and advancing knowledge in chronic thromboembolic PH (CTEPH). Table 1 provides a list of the abstracts and presenters featured during the session.[1–7] Notably, some of these studies have already made it to publication in peer-reviewed journals.[8–11]

In the sections that follow, we will focus on the five virtual mini-symposium themes by reviewing existing context-relevant knowledge, summarizing the abstracts presented, evaluating their strengths and limitations, and highlighting their potential clinical implications. Finally, we will discuss relevant priorities and future directions in PH clinical research.

Standardizing diagnosis and management of PH

PH is an ever-changing field where clinicians face a myriad of diagnostic and therapeutic challenges. Considerable heterogeneity exists in PH, which rarely presents as an isolated entity and is more often associated with one or more predisposing factors, exposures, or disease states. Rates of clinical disease progression and outcomes vary widely across patients, and even among specific forms of PH there is no uniformly effective treatment approach. As a result of these complexities, ongoing endeavors to refine and standardize disease diagnosis, classification and management approaches remain essential. Fortunately, ever since the first WSPH convened in 1973, there has been a collaborative effort in the clinical and scientific PH community to iteratively consolidate available evidence, identify areas of need, and generate recommendations. This consensus-based approach has fundamentally cultivated the research and therapeutic advancements achieved in the field. For adults with PH, the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines provide the most recent comprehensive diagnosis and treatment recommendations.[12] In 2018, the 6th World Symposium on Pulmonary Hypertension (WSPH) modified the hemodynamic definition of PH, refined the classification scheme, revised the diagnostic algorithm, and consolidated updated knowledge on available risk stratification tools and therapies.[13–15] Pediatric PH was not specifically addressed until the 2013 WSPH, yet consensus recommendations soon followed from the North American Pediatric Pulmonary Hypertension Network [16] and the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) [17] in 2015 and 2016, respectively. A pediatric task force convened at the 2018 WSPH to unify the definition of PH and facilitate pediatric to adult PH care transitions.[18] The EPPVDN recently published the most updated consensus statement available in the field,[8] which was highlighted by Dr. Eric Austin during the ATS mini-symposium.[1]

Table 1. Highlighted abstracts and presenters from the virtual mini-symposium "What's New in Pulmonary Hypertension Clinical Research: Lessons from the Best Abstracts at the 2020 American Thoracic Society International Conference."

Theme	Presenter	Abstract title
Standardizing diagnosis and management of PH	Austin, E.D.	2019 Updated Consensus Statement on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension: The EPPVDN [1]
Improving risk assessment in PAH	Benza, R.L.	Bayesian Network Modeling: The Future of Pulmonary Arterial Hypertension Risk Stratification Through the PHORA Initiative [2]
Evaluating biomarkers of disease activity	Peplinski, B.	Angiopoietin Associations Across the Cardiovascular Disease Spectrum: The MESA Angiogenesis Study [3]
	Synn, A.	Radiographic Pulmonary Vascular Pruning and Right Ventricular Function in the Framingham Heart Study [4]
Understanding metabolic dysregulation across the PH spectrum	Trammell, A.W.	Increased Risk of Death in Underweight and Normal Weight Patients with Pulmonary Hypertension [5]
	Hemnes, A.	PVDOMICS: Early Metabolic Findings Across the Spectrum of Pulmonary Hypertension [6]
Advancing knowledge in CTEPH	Kerr, K.M.	United States CTEPH Registry: Differences Between Operated and Non-Operated Subjects in Baseline Data and 1-year Outcomes [7]

Updated 2019 consensus statement on the diagnosis and treatment of pediatric PH (presented by Eric Austin, MD, Vanderbilt University).

The executive writing group for the updated EPPVDN statement was diversely composed, including 31 members from 11 countries with multi-disciplinary expertise spanning various pediatric and adult subspecialities. Building on the comprehensive 10-paper EPPVDN guidelines published in 2016, the update centered on Group 1 PAH. The authors conducted a PubMed/MEDLINE search (for the time period 1990–2018) and provided tabular recommendations across 10 clinical topic domains. The degree of consensus and level of evidence supporting each recommendation was formally graded according to the ESC/AHA system. Dr. Austin offered a broad-sweeping overview of these guidelines, concentrating on the significant updates and unique features of the document.

As expected, the 2019 EPPVDN statement incorporated changes to the hemodynamic definition and classification of PH from the 2018 WSPH. Recommendations were first provided in the general realm of diagnosis and monitoring, including a new pediatric PH diagnostic algorithm and user-friendly multiparametric risk evaluation tool that stratifies patients into low, intermediate, and high-risk categories. Some of the pediatric risk determinants mirror those found in the 2015 ESC/ERS adult risk assessment table, while others are unique (i.e. child growth, specific echocardiographic and cardiac magnetic resonance imaging (MRI) parameters, mean pulmonary arterial to systemic arterial pressure ratio, and vasoreactivity status). Although pediatric risk determinants are only backed by level C evidence (expert opinion and/or retrospective studies), available data indicate that World Health Organization (WHO) functional class, N-terminal-pro brain natriuretic peptide (NT-proBNP), and tricuspid annular plane systolic excursion (TAPSE) are associated with mortality and warrant further investigation as candidate intermediate endpoints.[8,19] Next, the EPPDVN statement evaluated multiple newly developed echocardiography parameters, including right ventricular outflow tract size and flow, right atrial function, pulmonary arterial acceleration time, and measurements reflective of ventricular–ventricular interaction. A concerted effort was made to standardize normal reference values for these markers in the pediatric population. Similar recommendations were provided in the cardiac MRI domain, which informed the selection of proper imaging modes and evaluated the utility of mode-specific assessments of right ventricular structure and function, afterload, fibrosis, pulmonary blood flow, and interventricular dyssynchrony. An algorithm for genetic counseling and testing was also developed for children with idiopathic or heritable PAH, and guidance was provided for family member testing and surveillance. Moreover, recommendations were given on the role of specific blood biomarkers (i.e. NT-proBNP, uric acid, circulating endothelial cells, endothelin-1, troponin, microRNA) in the appraisal of disease severity, progression, and response to therapy.

Few randomized controlled trials of therapeutics have been conducted in children with PAH, and treatment is primarily directed by expert experience and evidence extrapolated from adult studies. Nonetheless, the EPPDVN updated consensus statement devoted an extensive section to chronic therapy in pediatric PAH, with an updated treatment algorithm (Fig. 1) and a focus on drug–drug interactions. Recommendations supported early combination therapy for patients who are initially intermediate-risk (dual oral therapy +/− inhaled prostacyclin) or high-risk (dual oral therapy + parenteral prostacyclin), as well as for low-risk patients who have an inadequate response to initial therapy. For children with severe progressive PAH who clinically deteriorate despite recommended therapy, the guidelines endorsed early transplant referral. Atrial septostomy and reverse Potts shunt were recommended as potential bridges to transplant in selected cases, and reverse Potts shunt was also deemed a possible destination therapy when transplant is not an option. However, the appropriate subpopulation for these interventions is not well-defined. Beyond chronic management, the consensus statement had a new concentration on therapy for acute PH in the pediatric ICU. Recommendations supported targeted therapies to decrease right ventricular (RV) afterload in critically ill children (i.e. inhaled nitric oxide and/or parenteral prostanoids for severe PH, inhaled nitric oxide or iloprost for postoperative PH, oral sildenafil for rebound PH upon withdrawal of inhaled agents, etc.). Among children with cardiogenic shock or profound respiratory failure unresponsive to maximal medical therapy, extracorporeal life support was felt to be a final possible option as a bridge to transplant or recovery. Additional new sections in the 2019 EPPVDN document offered detailed guidance on (a) evaluation and management of PH in children with congenital heart disease (CHD) and (b) supportive measures and pharmacotherapy for persistent PH of the newborn and PH associated with bronchopulmonary dysplasia/chronic lung disease. Finally, a novel set of recommendations for the management of PH in middle- and low-income regions (MLIRs) was developed, which uniquely focused on resource-sensitive diagnostics, specific conditions (i.e. rheumatic heart disease, acquired lung diseases such as tuberculosis, human immunodeficiency virus, schistosomiasis), operability in late-presenting CHD, the use of phlebotomy and anticoagulation in Eisenmenger syndrome, and pregnancy counseling, among other issues. This section on MLIRs provides proof of a strong global perspective and spirit of inclusivity within the EPPVDN.

Although only three years had elapsed since the preceding EPPDVN consensus statement, the 2019 document provides a wealth of updated guidance. This yield reinforces the importance of frequent iterative efforts to standardize our approach to patient care in the rapidly evolving field of PH.

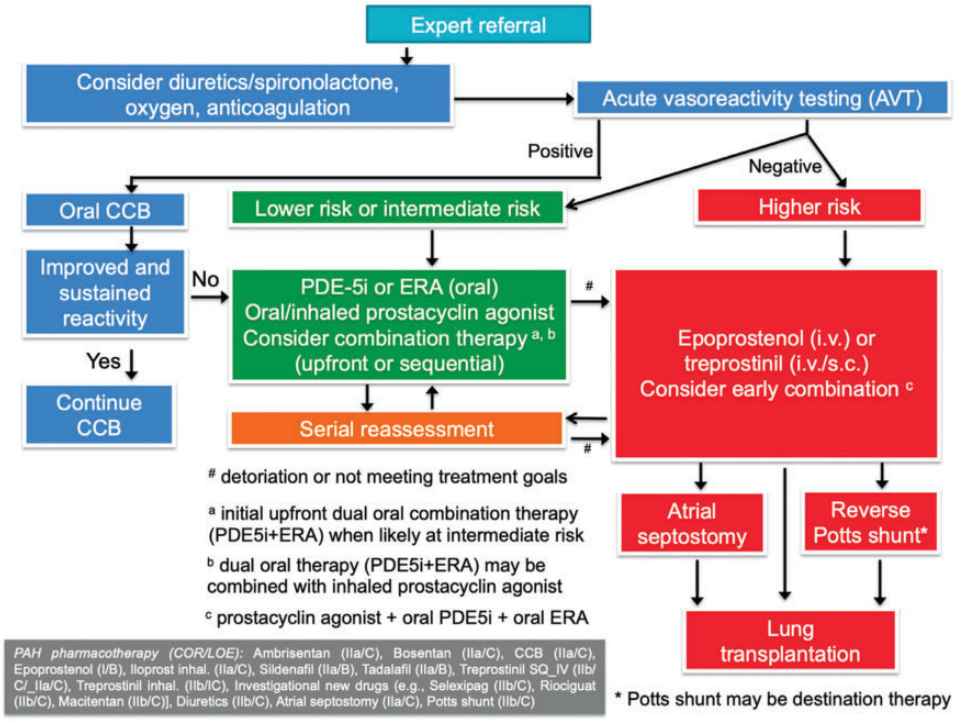

Fig. 1. European Pediatric Pulmonary Vascular Disease Network (EPPDVN) updated consensus treatment algorithm for pediatric PH. The guideline shown primarily applies to idiopathic and heritable PAH, as there are limited clinical data on therapy for other forms of pediatric PH. Most pulmonary vasodilator agents are considered off-label for pediatric PH, other than sildenafil (Europe) and bosentan (US and Europe). CCB: calcium channel blocker; COR: class of recommendation; DPAH: drug-induced pulmonary arterial hypertension; EMA: European Medicines Agency; ERA: endothelin receptor antagonist; ES: Eisenmenger syndrome; HPAH: heritable pulmonary arterial hypertension; inh.: inhalation; IPAH: idiopathic pulmonary arterial hypertension; i.v.: intravenously; LOE: level of evidence; PDE-5i: phosphodiesterase 5 inhibitor; s.c.: subcutaneously. Figure reprinted with permission from Hansmann et al.[8]

The EPPVDN executive writing group should be commended for crafting such a comprehensive, yet granular, set of recommendations in the face of limited high-quality evidence.

Improving PAH risk assessment

Prognostication has been long recognized as important in PAH, ever since a landmark National Institutes of Health (NIH) registry study first confirmed the high burden of mortality and identified predictors of risk three decades ago.[20] Risk assessment is a central element of modern PAH treatment guidelines and remains an active area of research.[12,21,22] Comprehensive risk assessment in PAH requires simultaneous consideration of multiple clinical features, as no single variable has been found to provide sufficient prognostic information.[12,23] The inadequacy of single variable risk stratification may in part relate to the heterogeneity of PAH subtypes, where underlying comorbidities and systemic factors can confound individual clinical risk predictors (i.e. 6MWD, functional class, renal function, etc.). A variety of multidimensional risk stratification models have been developed through analyses of observational registries in the United States (US) and Europe, yet each have limitations and there is no consensus regarding the best approach. These tools are underutilized in real-world practice where clinician intuition is often discordant from model-determined risk.[24] Experts call for more accurate risk stratification tools, which could translate to earlier identification of "rapid progressors," individualized treatment decisions, prompt tertiary care or transplant referrals, well-informed patients, better resource allocation, and enhanced clinical trial efficiency.[25]

The first multidimensional risk score calculator was derived using data from the US Registry to Evaluate Early and Long-Term PAH Management (REVEAL),[26] a mixed cohort encompassing incident and prevalent cases and the full range of PAH subtypes. The REVEAL calculator predicts probability of one-year survival and partitions five risk strata, on the basis of 12 clinical variables that include modifiable parameters (laboratory, functional, hemodynamic, and echocardiographic) and non-modifiable factors (age, sex, and PAH subtype). Traditional multivariable regression methods guided the selection, thresholding, and weighting of these variables in model development. The REVEAL score has been validated in a newly diagnosed cohort, external registries, and clinical trial datasets.[27,28] It also appears to stratify survival differences beyond one year and retains predictive performance when applied at follow-up later in the disease course.[29,30]

An updated REVEAL 2.0 calculator was recently developed by incorporating two additional variables (Fig. 2), revised cut-points for continuous predictors, and alterations in variable weighting, yet this refinement only yielded modest incremental predictive value [31] (c-statistic 0.76 vs. 0.74 for original calculator). It has not been clarified how the REVEAL risk calculator translates to treatment decisions, and the tool is perceived by some to lack feasibility given the large number of required input variables.[22] However, a simplified REVEAL "Lite" 2.0 model that incorporates only six modifiable parameters (NT-proBNP, WHO functional class, six-minute walk distance (6MWD), heart rate, systolic blood pressure, and glomerular filtration rate) was recently shown to approximate the full REVEAL model and retain good predictive performance.[32]

Subsequent to the original REVEAL analysis, the 2015 ESC/ERS guidelines introduced a risk assessment table that divides modifiable clinical parameters into low, intermediate, and high-risk categories.[12] The variables and cut-points dividing their risk silos were based on expert opinion, rather than being established through an agnostic data-driven approach. Using this ESC/ERS guideline table as a framework, composite risk stratification algorithms were developed in cohorts from the French PH Network [33] (FPHN), the Comparative Prospective Registry of Newly Initiated Therapies for PH [34] (COMPERA), and the Swedish PAH Register [35] (SPAHR). Notably, these cohorts were limited to incident cases of predominantly idiopathic PAH. Simplicity is a strength of the FPHN, COMPERA, and SPAHR algorithms, as the number of input parameters ranges from 4 to 8 across approaches (Fig. 2). Whether applied at baseline or at follow-up, these models stratify groups with clear differences in five-year survival. Also shown to identify PAH therapy "responders" who achieve low-risk status and exhibit a favorable prognosis,[33,36] European risk assessment

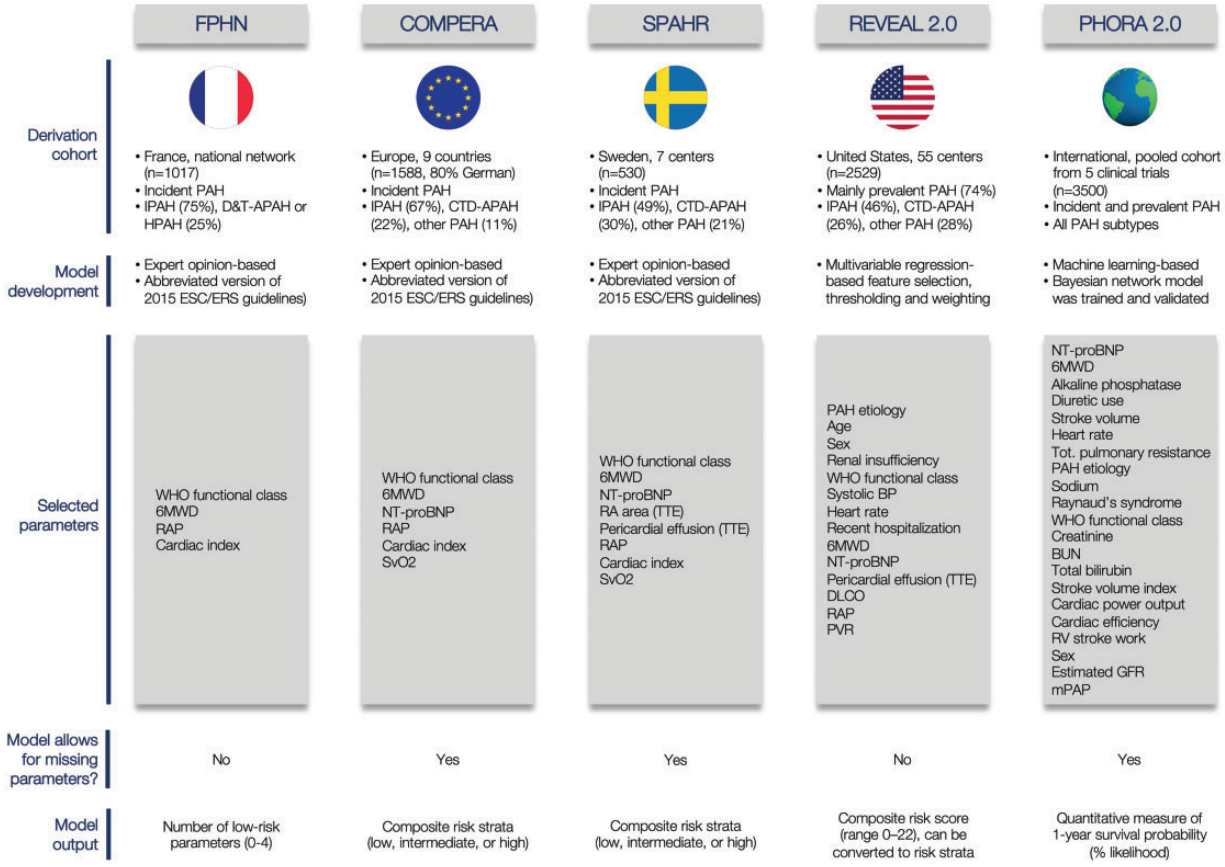

Fig. 2. Comparison of current PAH risk stratification tools. Tabular summary of five modern risk assessment tools, including the French Pulmonary Hypertension Network (FPHN), Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), and Swedish PAH Register (SPAHR) approaches, the Registry to Evaluate Early and Long-Term PAH Management (REVEAL) 2.0 calculator, and the unpublished Pulmonary Hypertension Outcomes Risk Assessment (PHORA) 2.0 model which was presented during the ATS virtual mini-symposium. 6MWD: six-minute walk distance; BP: blood pressure; BUN: blood urea nitrogen; CTD-APAH: connective tissue disease associated pulmonary arterial hypertension; DLCO: diffusion capacity for carbon monoxide; ESC/ERS: European Society of Cardiology/European Respiratory Society; GFR: glomerular filtration rate; HPAH: heritable pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RV: right ventricle; SVO2: mixed venous oxygen saturation; TTE: transthoracic echocardiogram; WHO: World Health Organization.

strategies have a well-defined role in recommended treatment algorithms.[22,37]

Much has been learned from the growing body of research in PAH risk stratification, yet available models at best only achieve fair to good discriminatory accuracy [31] (c-statistics range from 0.6 to 0.8). The registries utilized to develop these models shared several methodological shortcomings including their collection of limited sets of clinical variables, missing data, loss to follow-up, and retrospective validation analyses. Moreover, imbalances in derivation cohort characteristics (i.e. predominance of prevalent PAH cases in REVEAL registry, underrepresentation of certain PAH subtypes in European registries, lack of geographical and ethnic diversity, etc.) introduced sources of bias that may limit model generalizability in real-world populations. Established models were built on the assumption that predictors of clinical risk each have a linear and independent association with the outcome, while potentially important inter-predictor relationships were ignored. Finally, the existing approaches merely categorize patients into risk strata without providing a more precise quantitative measure of risk. As part of the ATS virtual mini-symposium, Dr. Raymond Benza presented work demonstrating that machine learning (ML) offers a promising methodological solution for the risk stratification challenge in PAH.

Bayesian network modeling: The future of PAH risk stratification through the PHORA initiative (presented by Raymond Benza, MD, Ohio State University)

Dr. Benza and his colleagues have recently developed a supervised ML-based tool for prediction of survival, known as the Pulmonary Hypertension Outcomes Risk Assessment (PHORA) model.[38] Supervised ML involves the use of computational algorithms to make predictions (i.e. determine probability of an outcome, classify a categorical feature, etc.) and/or identify interaction patterns among variables. Supervised ML algorithms require that data samples are labeled a priori (i.e. outcome or feature class is known), in contrast to unsupervised ML methods which infer otherwise hidden structure and patterns in unlabeled datasets. To develop the PHORA model, Dr. Benza and colleagues shrewdly selected the tree-augmented naïve (TAN) Bayes algorithm. This Bayesian network-based approach is particularly well-suited to the task at hand, providing a flexible but rigorous probabilistic framework that (a) handles both continuous and qualitative data, (b) accounts for linear or non-linear interactions between multiple variables and their interdependent effects on the outcome, and (c) offers predictions even when input data elements are missing.[39] In a recent published study,[38] the first iteration of the PHORA model was derived using the REVEAL cohort. Trained with the same set of input variables and cut-points required for the REVEAL 2.0 calculator, the TAN Bayes ML algorithm yielded an accurate model which outperformed REVEAL 2.0 (c-statistic 0.80 vs. 0.76 for prediction of death at one year). Bayesian network-based methodology has similarly achieved better predictive accuracy than traditional statistical models in other disease states.[40] This PHORA model retained performance even when patients had multiple missing variables, as is often the case in real-world practice. Furthermore, it exhibited external validity in the COMPERA cohort (c-statistic 0.74) and Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) registry (c-statistic 0.80).

Dr. Benza's ATS presentation highlighted an updated PHORA 2.0 model.[2] Avoiding the known limitations of registry data, PHORA 2.0 was developed using large datasets aggregated from contemporary clinical trials. Rather than anchoring to the same REVEAL-based input parameters and cut-points, the PHORA 2.0 model was built by incorporating both empirical methods and domain knowledge to select and refine variables with the greatest predictive power. A meta-analysis of five prior industry-sponsored trials of PAH vasodilator therapies ($n = 2800$) was conducted to select initial candidate input features, followed by feature engineering based on expert opinion. Using these selected features, a TAN Bayes model was trained to predict one-year survival in a harmonized Food and Drug Administration dataset pooled from contemporary PAH clinical trials ($n = 3500$): AMBITION (NCT01178073),[41] PATENT-1 (NCT00810693) and PATENT-2 (NCT00863681),[42] GRIPHON (NCT01106014),[43] SERAPHIN (NCT00660179),[44] and FREEDOM-EV (NCT01560624).[45] This harmonized cohort was divided into a training set for model derivation (80%) and a held-out test set for validation (20%). During model training, variables were further refined and discretized by feature learning (expectation maximization) across iterative algorithm runs, then a dimensionality reduction approach eliminated variables that were only predictive by chance. Finally, Bayesian network structure (variable interactions and joint probabilities) was learned on patients with no missing variables ($n = 541$), and final variables were learned on the full training set. Several aspects of this sophisticated approach safeguarded against model overfitting. The final PHORA 2.0 Bayesian network encompassed 21 clinical variables (Fig. 2), with NT-proBNP, 6MWD, alkaline phosphatase, diuretic use, and stroke volume as the top predictors. PHORA 2.0 achieved a c-statistic of 0.83 for predicting death in the unseen held-out validation test set, outperforming other models including PHORA 1.0 (c-statistic 0.77), REVEAL 2.0 (c-statistic 0.76), FHPR (c-statistic 0.59), and COMPERA (c-statistic 0.55).

Beyond predicting risk with a high degree of discrimination, the PHORA model offers an appealing probabilistic framework that can be visually represented in an intuitive and interactive format (www.myphora.org). This allows clinicians to input patient-specific clinical parameters at the point of care and obtain a quantitative absolute measure

of mortality risk, even when some input variables are not available (Fig. 3). The existing stratification approaches reliably identify low and high-risk PAH strata, yet these tools less accurately discriminate intermediate-risk patients.[23] Moreover, a recent study revealed that only one-half of intermediate-risk patients (stratified by REVEAL 2.0 and COMPERA scores) achieved the target low-risk profile after guideline-recommended treatment with upfront oral combination therapy.[46] A more granular assignment of risk along the continuum, such as that offered by PHORA, could potentially better inform therapy interventions (particularly in the intermediate-risk range). Although not yet validated for longitudinal use, PHORA's quantitative risk metric might also provide a more precise assessment of treatment response (relative risk reduction rather than change in stratum). To date, no study has demonstrated that a risk-guided intervention strategy translates to improved outcomes. There is a critical need to bridge the gap between future risk assessment tools, treatment decisions, and ultimately outcomes. PHORA 2.0 is undeniably the most sophisticated PAH risk assessment tool developed, yet like its predecessors it does not include "deep" phenotypic variables with known prognostic significance (advanced echocardiographic and cardiac MRI parameters, cardiopulmonary exercise test metrics, vascular imaging features, novel biomarkers, etc.). The PAH community is still working to determine the optimal balance between ease-of-use and sophistication in a risk model.

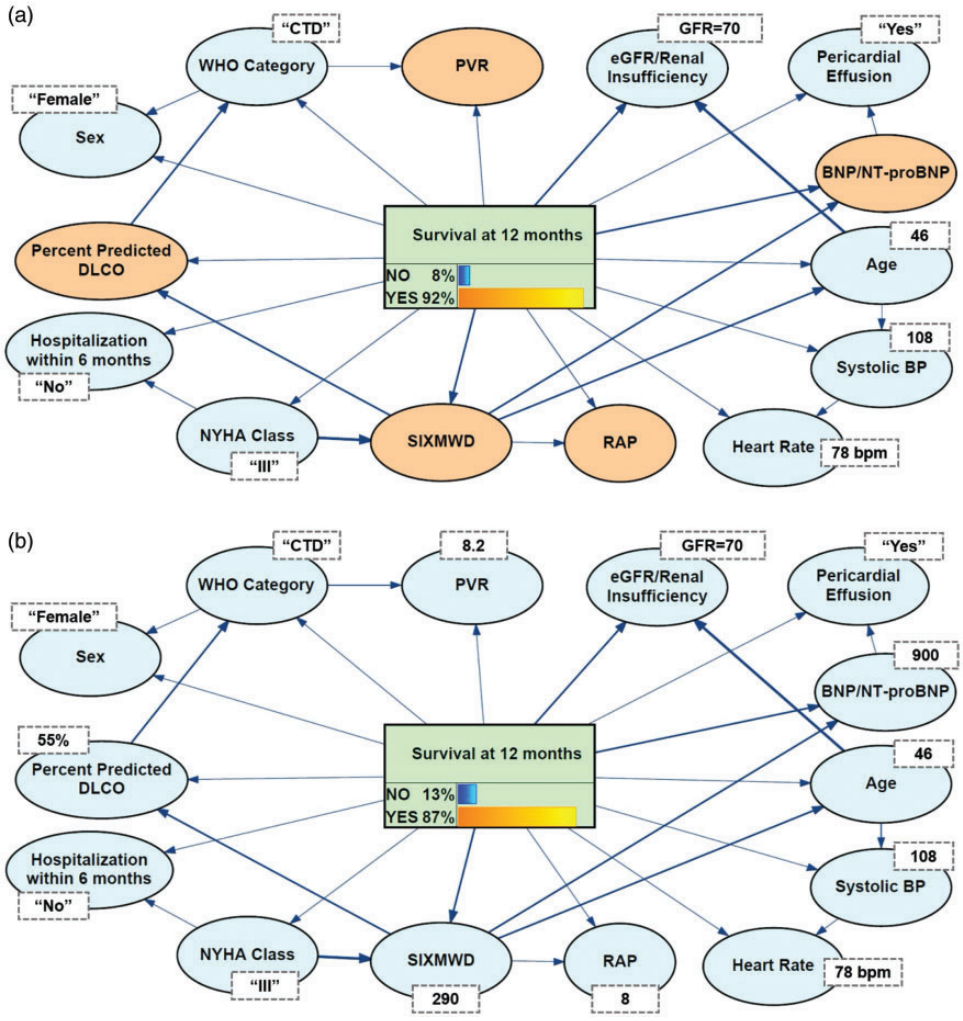

Fig. 3. Graphical representation of Pulmonary Hypertension Outcomes Risk Assessment (PHORA) model. (a) Network visualization of the PHORA 1.0 model for an example patient with missing/unavailable input parameters. The values of known input variables (blue) are shown within inset dashed boxes, while values of unknown variables (orange) have not yet been obtained for this sample patient. The model ouput (predicted probability of one-year survival) is shown in the center box (green). (b) Updated PHORA model output when all input parameters are available. In both networks, the thickness of directed edges connecting nodes reflects the strength of interrelationships between variables. BP: blood pressure; CTD: connective tissue disease; DLCO: diffusion capacity of lung for carbon monoxide; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal brain natriuretic peptide; NYHA: New York Heart Association; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SIXMWD: six-minute walk distance. Figure courtesy of Dr. Raymond Benza, Ohio State University Wexner Medical Center.

Evaluating biomarkers of disease activity

The development of accurate, informative, and practical non-invasive biomarkers is of particular interest in PAH, as frequent hemodynamic assessments and tissue sampling at the disease site are not feasible. Broadly speaking, PAH biomarkers seek to fulfill one or more of the following purposes: (a) determine diagnosis (i.e. early discrimination or disease subtyping), (b) evaluate prognosis (i.e. stratify clinical severity and mortality risk), (c) act as surrogate endpoints (i.e. monitor treatment effect), or (d) predict response to therapy.[47] While most biomarker studies in PAH have centered on diagnosis, prognosis, and surrogate end-points, there is a critical unmet need to identify predictors of therapy response.

A few blood biomarkers are used in clinical practice to assist PAH diagnosis and subtyping, including genetic mutations. After bone morphogenetic receptor type 2 (*BMPR2*) mutations were found to underlie 80% of hereditary PAH cases and occur in 10–15% of idiopathic PAH patients,[48] next-generation sequencing led to discovery of several more genes associated with hereditary PAH or pulmonary veno-occlusive disease.[49] The most studied and widely adopted prognostic circulating biomarker is brain natriuretic peptide (BNP or NT-proBNP), which correlates with several indicators of disease severity (hemodynamics, exercise metrics, and RV imaging parameters), strongly predicts mortality risk, and is associated with clinical changes over time.[50–52] BNP and NT-proBNP are the only blood biomarkers recommended by clinical guidelines, both at diagnosis and during treatment to dynamically prognosticate and monitor therapy response.[12]

Numerous other promising diagnostic and/or prognostic blood biomarkers have been proposed, yet the large majority are not utilized in patient care. Poor feasibility or inadequate validation are often cited as the barriers to clinical implementation. Candidate circulating biomarkers reported include those related to heart failure (uric acid, bilirubin, GDF15, hepatocyte growth factor, etc.),[53–56] markers of inflammation (various cytokines and chemokines, c-reactive protein, soluble CD40 ligand, osteopontin, etc.),[57–61] growth factors (VEGF, PDGF, TGF-beta, etc.),[62–64] mediators of vascular smooth muscle tone (adrenomedullin, asymmetric dimethylarginine, etc.),[65,66] indicators of vascular remodeling (multiple adhesion factors, matrix metalloproteinases, etc.),[67,68] clotting factors (von Willebrand factor, thromboxane B2, etc.),[69] and red cell distribution width,[70] among others. Recently, high-throughput "-omics" screening strategies have uncovered multiplex biomarker signatures of PAH. In a compelling multi-cohort European proteome study of idiopathic and hereditary PAH,[71] aptamer-based assay screening (>1100 proteins) identified a 9-biomarker signature (ILR4, Epo, factor D, IGFBP-1, TIMP2, TIMP1, Factor H, plasminogen, ApoE) that strongly predicts survival independent of NT-proBNP and the REVEAL risk score. Importantly, changes in this biomarker profile over time were shown to add prognostic value. Additional multiplex blood signatures that discriminate PAH have been discovered through untargeted analyses of the transcriptome (whole blood and mononuclear cells),[72,73] metabolome,[74] microRNAs,[75] and circulating endothelial or mononuclear cell subpopulations.[76–78] While these multiplex signatures are not yet adopted in routine clinical care, they have afforded insights into signaling pathways regulated in PAH.

There is increasing interest in the use of echocardiography, cardiac MRI, and lung imaging modalities to identify biomarkers. Transthoracic echocardiography (TTE) is the initial test of choice when evaluating patients with suspected PH, as several TTE measurements are established as diagnostic biomarkers that determine the probability of PH and help differentiate pre from post-capillary PH.[12,79] Multiple TTE biomarkers are also utilized in practice to prognosticate and gauge treatment response, such as right atrial area, right ventricular (RV) fractional area change, TAPSE, and the presence of pericardial effusion.[80] Other parameters, including RV free wall strain and the myocardial performance (Tei) index, are not universally adopted but are viable surrogate endpoints given their correlation with MRI-determined RV function and pulmonary vascular resistance (PVR).[81,82] Although TTE is widely available and cost-effective, cardiac MRI provides more accurate and reproducible quantitative RV assessments across repeated studies. Thus, there is growing enthusiasm around MRI measurements of RV morphology and function, pulmonary arterial stiffness, and ventriculoarterial coupling as surrogate end-points.[80] Chest computed tomography (CT) is commonly performed to phenotype patients undergoing PH evaluation. This modality can detect parenchymal lung processes, thromboembolic disease, congenital anomalies, mediastinal abnormalities, or signs of pulmonary veno-occlusive disease that inform prognosis and dictate therapeutic options.[83] Technological advancements in CT image acquisition, reconstruction, and processing have translated to enhanced visualization of the pulmonary vasculature and automated quantitative metrics of vascular remodeling. For example, CT-based measures of vessel tortuosity and pruning have been shown to correlate with hemodynamic parameters in PAH and CTEPH.[84,85] In the future, these CT markers of vascular remodeling might facilitate early diagnosis or serve as novel end-points in studies of disease-modifying therapies. Finally, emerging data highlight other advanced imaging modalities that could be applied to evaluate biological processes implicated in PAH vasculopathy (i.e. molecular-targeted PET) or offer dynamic physiological assessments of blood flow distribution (i.e. dual-energy CT, 4D flow MRI, and MRI ventilation and perfusion sequences).[86]

The ATS virtual mini-symposium featured two exciting abstracts focused on biomarkers, including a study which examined the implications of circulating angiopoietin in

both right and left heart failure, and another which investigated an automated CT measure of pulmonary vascular pruning.

Angiopoietin associations across the cardiovascular disease spectrum: The MESA angiogenesis study (presented by Brandon Peplinkski, MD, University of Washington)

Angiopoietin signaling plays an important role in preserving vascular homeostasis and normal angiogenesis in multiple organs. Two forms of angiopoietin, angiopoietin 1 (Ang1) and angiopoietin 2 (Ang2) have been implicated in various cardiovascular diseases and appear to have opposing effects. Mechanistic studies indicate that Ang1 promotes blood vessel survival and stabilization, whereas Ang2 can induce vascular destabilization, increased permeability and abnormal endothelial cell proliferation in certain contexts.[87,88] Early angiopoietin research in congestive heart failure patients found that Ang2 was overexpressed, while Ang1 levels were normal in peripheral blood.[89] More recent work demonstrates that elevated Ang2 levels in both acute and chronic heart failure are associated with increased disease severity and worse prognosis.[90–93] However, it remains unknown whether Ang2 contributes to the development of heart failure, reflects adaptation to heart failure, or represents an epiphenomenon.

This fundamental question was an overarching motivation for the work presented by Dr. Peplinski and colleagues.[3,9] In their innovative study design, levels of angiopoietin 2 were evaluated in three different populations – (1) subjects from the large multicenter Multi-Ethnic Study of Atherosclerosis (MESA) cohort who did not have overt cardiovascular disease at enrollment and were followed for the development of incident heart failure, (2) a PAH cohort with chronic right heart failure recruited at the University of Washington (Seattle, WA), and (3) patients with established biventricular heart failure recruited at the Medical University of South Carolina (Charleston, SC).

In the MESA population, which in its entirety includes more than 6000 subjects from six communities in the US,[94] baseline Ang2 measurements were available for 1358 subjects. Linear regression models were used to assess associations between Ang2 and cardiac MRI parameters at enrollment, and Cox proportional hazards models were fitted to evaluate the relationship of baseline Ang2 with incident heart failure or death during follow-up. Models were adjusted for age, sex, height, weight, site of enrollment, education, race/ethnicity, blood pressure, tobacco use, diabetes, and cholesterol levels. No significant relationships were found between Ang2 and any measures of cardiac morphology or function, which included right and left ventricular end diastolic mass, end diastolic volume, stroke volume, and ejection fraction. Although Ang2 was not associated with cardiac parameters at enrollment, elevated baseline levels did portend increased risk of incident heart failure or cardiovascular death during follow-up (hazard ratio 1.21 per one standard deviation increase in Ang2, $p < 0.001$) (Fig. 4).

The PAH cohort analyzed by Dr. Peplinski and colleagues included 73 patients recruited at the University of Washington. Linear regression and Cox proportional hazards models were again fitted to evaluate Ang2 relationships with (a) hemodynamic parameters measured by right heart catheterization and (b) survival, respectively. Models were adjusted for age, sex, race/ethnicity, and PAH etiology. A positive association was detected between Ang2 and right atrial pressure (RAP) (1.8 mmHg increase in RAP per one standard deviation increase in Ang2). No significant relationships were found between Ang2 and systolic blood pressure, pulmonary arterial wedge pressure (PAWP), mean pulmonary arterial pressure (mPAP), PVR, or cardiac index (CI). Nonetheless, elevated Ang2 levels were associated with increased mortality risk (hazard ratio 1.9 per one standard deviation increase in Ang2). These findings reinforce data from a prior study of idiopathic PAH ($n = 81$) which also supported Ang2 as a marker of PAH severity and outcomes.[95] In this previous study, Ang2 levels positively correlated with hemodynamic parameters (RAP, mPAP, PVR, CI), were prognostic of survival and appeared to track with clinical markers of improvement or deterioration after PAH therapy initiation.

The final study cohort included 57 patients with prevalent biventricular failure recruited at the Medical University of South Carolina. Similar to the analyses performed in the PAH cohort, models were fitted to assess Ang2 associations with hemodynamic parameters (linear regression) and the combined outcome of death, transplant, or LVAD (Cox proportional hazards regression). The models were adjusted for the same covariates as in the PAH cohort, but the etiology of left heart disease substituted PAH etiology. Among these biventricular heart failure patients, Ang2 was significantly associated with PAWP (3.4 mmHg increase per one standard deviation increase in Ang2) in addition to RAP (2.7 mmHg increase per one standard deviation increase in Ang2). However, no significant relationships were found between Ang2 and other hemodynamic measures (mPAP, PVR, CI) or risk of death, transplant, or LVAD placement.

Dr. Peplinkski and colleagues should be congratulated for their innovative study design, involving analyses of three complementary cohorts. Their most provocative and impactful data emerged from the multi-ethnic MESA cohort where elevated baseline Ang2 levels were associated with increased risk of incident heart failure. These findings suggest that Ang2 might play a role in the development of heart failure, rather than reflecting an adaptation to heart failure or an epiphenomenon. Nonetheless, this conclusion is speculative since causality cannot be established from association alone. Findings in the smaller PAH and

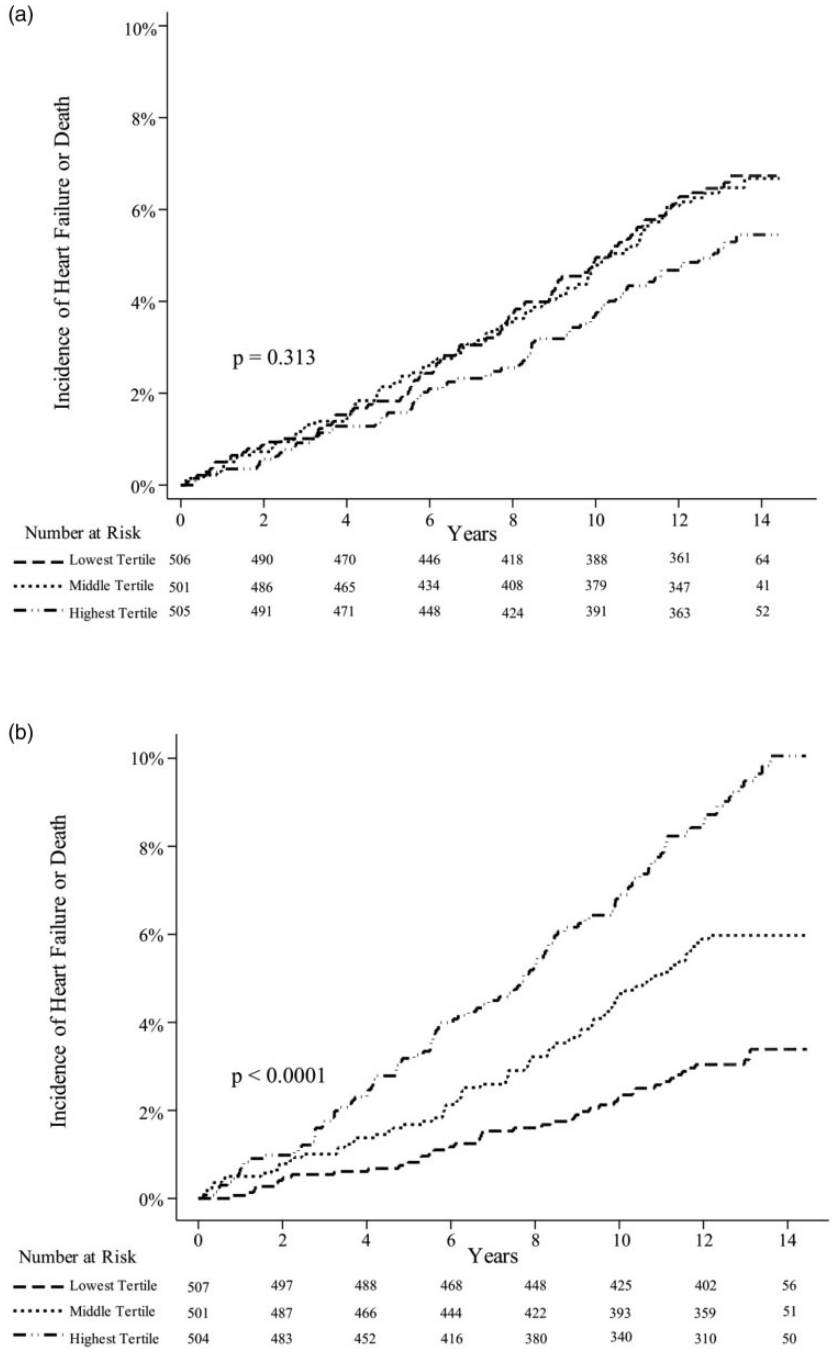

Fig. 4. Relationship between circulating angiopoeitin isoform levels and incident heart failure or death in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort. Kaplan–Meier curves show the probability of incident heart failure and death over time according to blood tertiles of (a) angiopoeitin-1 (Ang1) and (b) angiopoeitin-2 (Ang2) measured at study baseline. The number of subjects remaining at risk during follow-up is shown, and *p*-values reflect the log-rank test. Figure reprinted with permission from Peplinski et al.[9]

biventricular heart failure cohorts confirmed prior evidence that Ang2 is associated with heart failure severity regardless of the cause. These findings suggest a stronger Ang2 association with atrial volume overload than with increased ventricular afterload. Further research is warranted to investigate Ang2 as a prognostic biomarker and surrogate end-point in a larger prospective multicenter PAH cohort.

Radiographic pulmonary vascular pruning and right ventricular function in the Framingham Heart Study (presented by Andrew Synn, MD, Beth Israel Deaconess Medical Center)

In their abstract,[4] Dr. Andrew Synn and colleagues examined the association of a non-contrast CT measure of pulmonary vascular pruning to right heart morphology and

function in the Framingham Heart Study, a large population-based dataset.[96] "Pruning" describes the relative loss of small pulmonary arteries and contributes to an overall reduction in pulmonary vascular cross-sectional diameter. This phenomenon is a well-documented feature of PAH and is thought to result from increased endothelial cell apoptosis, but the underlying biological mechanisms are not fully elucidated.[97] Pruning has also been described in CTEPH and in PH due to left heart disease (WSPH Group 2) or chronic lung disease (WSPH Group 3).[98,99] Automated CT-based measures of pruning have not only been shown to correlate with disease severity in PAH and CTEPH,[84,85] but they were also found to be associated with RV remodeling and mortality risk in patients with tobacco exposure and chronic lung disease.[100,101] Moreover, in their prior work, Dr. Synn and colleagues reported on the associations of CT pruning with cigarette smoke exposure, lung function, and interstitial abnormalities in the Framingham cohort.[102–104]

Given that their previous work centered on cohorts enriched for heart and lung diseases, Dr. Synn and colleagues sought to determine whether vascular pruning is associated with subclinical RV dysfunction in a healthier population. The study cohort included 901 patients from the Framingham Heart Study Offspring Cohort who underwent cardiac MRI (between 2002 and 2006) as well as chest CT (between 2008 and 2011). The average patient age was 68.7 ± 8.6 years, and 55.2% of subjects were female. As intended, the prevalence of cardiopulmonary disease was relatively low; 5.3% of patients had congestive heart failure, 11.1% had a prior myocardial infarction, 29.3% had mild obstructive ventilatory defects by spirometry, and 17.9% had CT evidence of emphysema. Automated analyses of CT scans were performed by employing a well-validated algorithm encompassed by the Chest Imaging Platform (www.chestimagingplatform.com).[105,106] This algorithm reconstructs each CT to quantify the total vascular blood volume (TBV) and small vascular blood volume in vessels with cross-section $<5\,mm^2$ (BV5) (Fig. 5a). These volumes were used to calculate the BV5 to TBV ratio (BV5/TBV), which served as the marker of pulmonary vascular pruning. Cardiac MRI parameters of RV structure and function were obtained including end-diastolic volume (RVEDV), end-systolic volume (RVESV), and ejection fraction (RVEF). To evaluate the relationship between CT-determined vascular pruning (BV5/TBV) and RV parameters, the authors fitted multivariable linear regression models adjusted for age, sex, height, weight, smoking status, magnitude of smoking exposure (pack-years), occupation, education, and income level of the subject's neighborhood. Secondary linear models additionally adjusted for cardiovascular disease (myocardial infarction, heart failure, or ischemic stroke), left atrial size, and lung function metrics (forced expiratory volume in 1st second and diffusion capacity for carbon monoxide). Finally, generalized additive models with penalized splines were built to evaluate for non-linear pruning–RV associations.

In the primary multivariable regression analysis, more severe vascular pruning (lower BV5/TBV) was associated with larger RV volumes and worse RV function. For each standard deviation decrease in BV5/TBV, RVEDV increased by 6.0 mL (95% CI 4.1–7.9 mL, $p < 0.001$), RVESV increased by 3.3 mL (2.2–4.5 mL, $p < 0.0001$), and RVEF decreased by 1.0% (0.4–1.6%, $p = 0.0006$). The relationship between vascular pruning and RV function was linear (Fig. 5b). All associations retained significance after additional adjustment for cardiovascular disease, left atrial volume, and lung function.

In summary, more severe CT-based vascular pruning was independently associated with significant (but modest) differences in RV structure and function in a relatively healthy population-based cohort. The presenter acknowledged limitations. First, causality could not be inferred from the cross-sectional study design. It remains unknown whether the observed modest RV changes represent dysfunction or physiologic adaptation to increased afterload. Additionally, hemodynamic parameters were not measured and the relationship of pruning to borderline or subclinical PH could not be examined. Finally, left ventricle MRI parameters were not analyzed, but the authors intend to incorporate these data to understand interrelationships between pruning, the left ventricle and the RV in this population.[107,108] Ultimately, the BV5/TBV ratio appears to offer a feasible way to detect early remodeling and subtle changes in the pulmonary vasculature.

Understanding metabolic dysregulation across the PH spectrum

Preclinical studies have shown that metabolic dysregulation, particularly insulin resistance and altered lipid metabolism, promote pulmonary vascular disease. Comorbid conditions including obesity and diabetes are prevalent in patients with PAH.[109] Multiple small observational studies have found that prognosis is worse among PAH patients who have concomitant diabetes.[109,110] Prior evidence also signals that the "obesity paradox" is applicable in PAH, a phenomenon that has been described in multiple other cardiovascular disease states.[111] Although obesity is common in PAH and associated with more significant functional impairment early in the disease course, obese patients paradoxically have better survival than those with normal weight.[109,112] While obesity has been linked to insulin resistance in non-diabetic individuals, evidence suggests that the increased level of insulin resistance observed in PAH is not attributed to obesity.[113–115] The association between PAH and insulin resistance has been demonstrated across multiple studies. In one study where the triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio was used to define insulin resistance, female PAH patients were significantly more

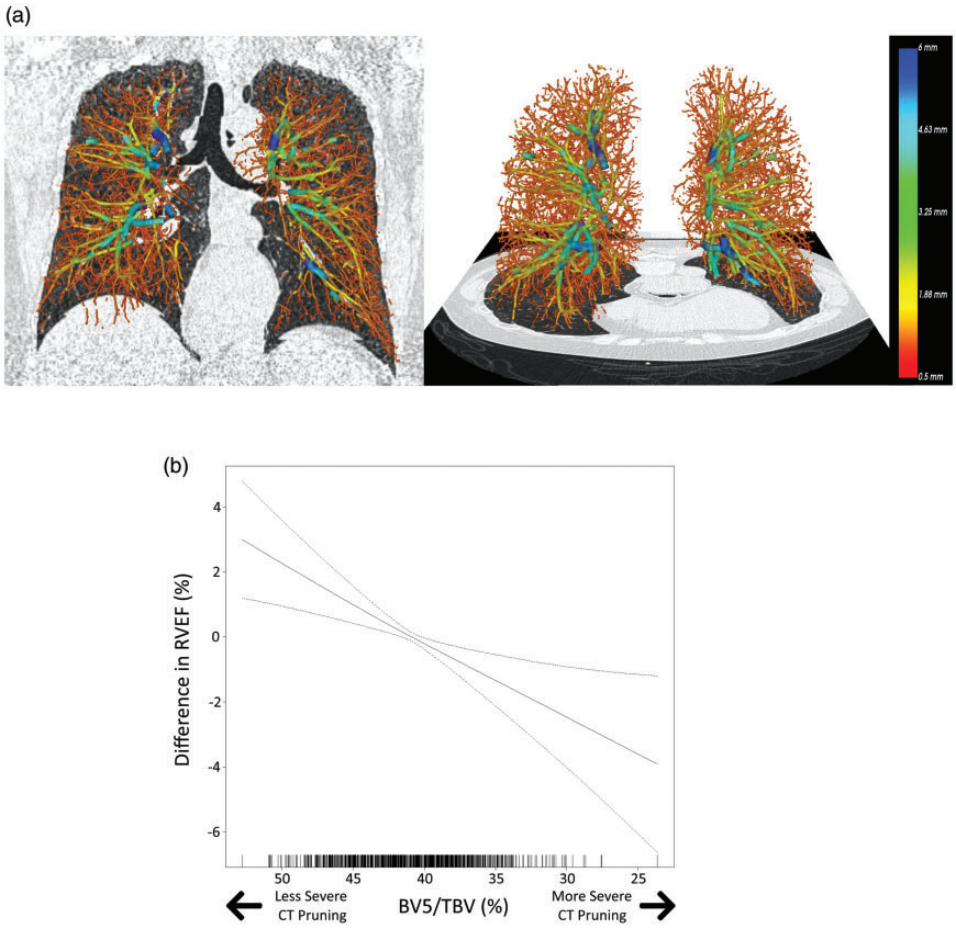

Fig. 5. An automated computed tomography (CT) measure of pulmonary vascular pruning (BV5/TBV) is associated with subclinical changes in right ventricular function in the Framingham Heart Study. (a) Example pulmonary vascular reconstruction from a participant in the cohort, overlaid onto a coronal (left) and axial (right) CT slice. The vessels are color-coded based on their diameter, with blue signifying large and red indicating small vessels. (b) Difference in right ventricular ejection fraction as a function of BV5/TBV (lower BV5/TBV values indicate more severe vascular pruning). Data reflect a penalized spline model (1.2 degrees of freedom) adjusted for age, sex, height, smoking status, pack-years of smoking exposure, occupation, education, and neighborhood income. Dashed lines represent the 95% confidence interval for the adjusted RVEF difference. The BV5/TBV distribution in the cohort is shown by a rug plot along the x-axis. Figures courtesy of Dr. Andrew Synn, Beth Israel Deaconess Medical Center.

likely to be insulin resistant than females from the general population; however, obesity alone did not account for this increased prevalence of insulin resistance.[116] In a different study, lower levels of HDL-C were not only observed in PAH patients but also predicted clinical worsening and increased mortality.[117] These associations between HDL-C and outcomes were not explained by interactions with age or obesity, and measures of the homeostatic model assessment of insulin resistance (HOMA-IR) were similar among PAH patients and healthy controls. In yet another PAH cohort of patients who did not have known diabetes, hemoglobin A1c screening again uncovered a high rate of insulin resistance that was independent of body mass index (BMI).[118] Abnormal fatty acid metabolism is also a recognized feature of PAH, as fatty acid accumulation has been observed in the myocardium of patients.[119] Recent work demonstrates a shift towards lipid and ketone metabolism at the expense of glucose control, perhaps as an adaptive response to supply the failing cardiac tissue with an additional source of energy.[120] Building on this body of work implicating dysregulated metabolism in PAH, Drs. Aaron Trammell and Anna Hemnes each presented studies which investigated metabolic features of PH across the spectrum of WSPH subgroups.

Increased risk of death in underweight and normal weight patients with pulmonary hypertension (presented by Aaron Trammell, MD, Emory University)

To investigate the potential effects of diabetes and weight on mortality risk in PH, Dr. Trammell and colleagues studied a large retrospective Veterans Health Administration cohort.[5,10] Veterans diagnosed with any subtype of PH between 2003 and 2015 were included in analysis

($n = 110{,}495$). Most patients were male (97%) and median age was 70.2 (IQR 62.1–79.6) years at the time of PH diagnosis. Over one-third (36.2%) of these veterans had diabetes mellitus and 73% were either overweight or obese at baseline. The cohort was mainly comprised of patients with PH due to multiple causes (57.6%), left heart disease (16.6%, WSPH Group 2), or chronic lung disease (16.6%, WSPH Group 3), while only a small proportion had WSPH Group 1 PAH (8.0%). Multivariable Cox proportional hazards models were fitted to assess the associations of diabetes and BMI with all-cause mortality. Sensitivity analyses assessed for a time-dependent relationship between BMI and outcome.

Diabetic patients had a 31% increase in risk of death relative to non-diabetic patients (HR 1.31, 95% CI 1.28–1.33, $p < 0.001$) after adjustment for age, sex, race, baseline BMI, and PH subtype (Fig. 6a). Overweight and obese patients both had a reduced risk of death by 29% and 44%, respectively, as compared to normal weight patients after adjusting for age, sex, race, PH subtype, and presence of diabetes (HR 0.71, 95% CI 0.70–0.72, $p < 0.001$, and HR 0.56, 95% CI 0.55–0.57, $p < 0.001$, respectively). On the other hand, underweight patients had a higher risk of death as compared to normal weight patients (HR 1.73, 95% CI 1.66–1.81, $p < 0.001$) (Fig. 6b). The effect of BMI on survival was observed regardless of the PH subtype or weight trend prior to PH diagnosis, and this association persisted in sensitivity analyses and upon adjustment for the Elixhauser comorbidity index [121] (a composite score of disease burden risk). The relationship of BMI with survival was non-linear across the BMI spectrum, with a sharp increase in risk as BMI transitioned from the normal to underweight range (Fig. 6c).

The authors should be commended for conducting this large-scale study, yet there are limitations which merit discussion. The population was almost exclusively male and

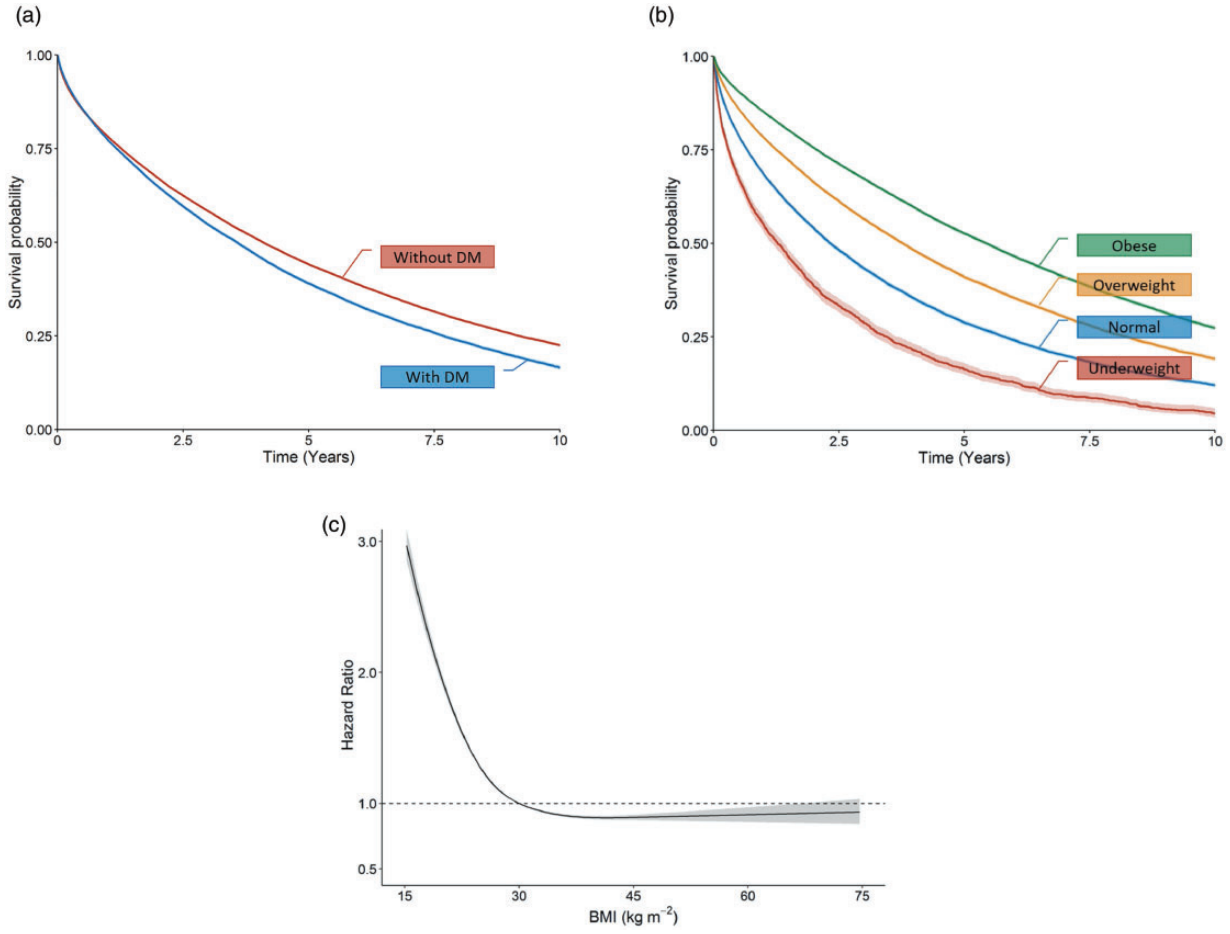

Fig. 6. The impact of diabetes mellitus and body mass index on survival in Veterans diagnosed with PH. (a) Kaplan–Meier estimates of all-cause 10-year survival for PH patients with comorbid diabetes mellitus (blue, $n = 40{,}040$) and without diabetes mellitus (red, $n = 70{,}455$). Survival was worse among diabetics (log-rank $p = 0.0001$). (b) Estimated survival probability according to body mass index (BMI) category: obese (green), overweight (orange), normal (blue), and underweight (red). Higher BMI categories had improved survival (log-rank $p < 0.0001$ across-classes). (c) All-cause mortality risk shown as a function of BMI (restricted cubic spline model adjusted for age, sex, race, PH subtype, and presence of diabetes). A non-linear relationship was observed between BMI and survival, with mortality risk increasing significantly as BMI transitions from normal to underweight. Figures reprinted with permission from Trammell et al.[10]

older than most PH cohorts, thus the findings may not be generalizable. Diagnoses of PH and comorbid conditions were based solely on ICD-9 codes, introducing possible misclassification. Moreover, potentially important adjustment covariates were not available for inclusion in survival models, such as smoking status. Because smokers have higher mortality rates and tend to have lower BMI, inadequate adjustment for smoking could bias results with underestimation of risk in overweight and obese subjects.[122,123] Nonetheless, the study from Dr. Trammell and colleagues is not only the largest investigation of obesity and PH survival to date, but also the first to expand analysis beyond WSPH Group 1 PAH. Their finding of improved survival among overweight and obese PH patients is in agreement with data from prior PAH cohorts.[109,112] During his presentation, Dr. Trammell cautioned that a causal relationship cannot be confirmed between BMI and mortality risk. Moreover, the findings do not suggest that weight gain is beneficial and translates to better PH outcomes. It is known that unintentional weight loss can accompany declining health and may contribute to poor chronic disease outcomes,[111] while conversely, adipokines released from excess adipose tissue may exert protective endocrine and paracrine effects.[124] One could speculate that these phenomena may in part explain the observed paradoxical relationships between BMI and PH outcomes. It is also important to consider that the longer survival observed in obese patients may not equate to improved quality of life. Overweight and obese PAH patients in the Pulmonary Hypertension Association Registry (PHAR), relative to their normal weight counterparts, had worse health-related quality of life measures and more frequent hospitalizations despite a lower mortality risk.[112] The findings of Dr. Trammell's study are provocative and highlight the need for more research to better elucidate how metabolic disorders and their treatment interact with PH.

PVDOMICS: Early metabolic findings across the spectrum of pulmonary hypertension (presented by Anna Hemnes, MD, Vanderbilt University)

The "Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics (PVDOMICS)" initiative is a multicenter NIH/NHLBI study seeking to re-examine the current PH clinical classification scheme by integrating clinical, physiological, and molecular data to redefine new phenotypes on the basis of shared multi-omics features.[125] Leveraging clinical phenotypic data from subjects in this contemporary PVDOMICS cohort, Dr. Hemnes and colleagues conducted a preliminary analysis which aimed to assess the prevalence of metabolic disease across the spectrum of PH subtypes. Starting in November 2016, PVDOMICs began enrolling three groups of subjects at seven U.S. centers: (1) patients with incident or prevalent PH, (2) diseased comparators with underlying heart, lung, blood, or sleep disorders who were found to have mPAP < 25 mmHg at right heart catheterization, and (3) healthy controls. Participants were extensively evaluated through a strict phenotyping protocol, which included history and physical examination, cardiac imaging with multiple modalities, pulmonary function assessment, 6-min walk and cardiopulmonary exercise testing, right heart catheterization, and multi-omics profiling. Patients with confirmed PH were assigned WSPH diagnostic classifications, as adjudicated by a central committee. The comparator subjects were further sub-divided into groups with borderline PH (mPAP 20–25 mmHg) and normal hemodynamics (mPAP < 20 mmHg). Age-, sex-, and race- matched healthy controls were recruited from the community and underwent the same phenotyping protocol, with the exception of right heart catheterization.

Dr. Hemnes presented metabolic findings from subjects who had completed the PVDOMICs protocol by the time of the ATS virtual mini-symposium. The study population consisted of 96 healthy controls, 334 diseased comparators, and 763 patients with PH (Table 2). The comparator and PH groups were older than the healthy controls despite age-matching (61 vs. 58 vs. 48 years, respectively, $p < 0.001$). The comparator and PH groups had higher BMI (30.4 vs. 30.3 vs. 27.6 kg/m^2, respectively, $p < 0.001$) and greater waist to hip circumference ratio (0.92 vs. 0.93 vs. 0.86, $p < 0.001$), but the percent body fat did not differ across groups (32 vs. 33 vs. 35%, $p = 0.11$). Systemic hypertension and diabetes were more prevalent in the comparator and PH groups than among healthy controls. Insulin resistance was also greater in comparator and PH groups than in healthy controls, as determined by the TG/HDL ratio (2.1 vs. 2.1 vs. 1.3, respectively, $p < 0.001$). However, another measurement of insulin resistance, the cross product of insulin and glucose (HOMA-IR), was higher in the comparator group than in PH patients or healthy controls (2.9 vs. 2.4 vs. 2.3, respectively, $p = 0.007$). In analysis of metabolic features by WSPH subgroup (Table 3), Group 2 PH patients had the highest BMI (mean 33.7 kg/m^2) and Group 2 and Group 3 had the highest percent body fat (38.1 and 32.9%, respectively). Insulin resistance by HOMA-IR was highest in Group 2 followed by Group 3 PH (3.0 and 2.8, respectively). The TG/HDL ratio was elevated among all PH subtypes, though no significant differences were observed across subtypes.

In summary, a high prevalence of metabolic disease was observed across PH subtypes and in comparators relative to healthy controls. Similar findings have been reported in other PH studies, and metabolic abnormalities are commonly encountered in chronic heart and lung diseases associated with Group 2 and 3 PH.[10,126] Increased insulin resistance was found across the spectrum of the PH population in PVDOMICS, among Group 1 PAH and particularly Group 2 and Group 3 PH. This study also confirms the finding that insulin resistance is primarily driven through the lipid axis, as illustrated by prior research. However,

Table 2. Clinical and laboratory metabolic features for subjects with PH, diseased comparators without PH, and healthy controls in the PVDOMICs cohort.

	Healthy controls ($n = 96$)	Diseased comparators ($n = 334$)	PH ($n = 763$)	p-value
Clinical				
Age, years	47.9 ± 14.3	60.7 ± 12.9	58.4 ± 14.7	<0.001
Sex, % female	67 (69.8)	193 (57.8)	483 (63.2)	0.66
Body mass index, kg/m^2	27.6 ± 5.7	30.4 ± 7.4	30.3 ± 8.1	<0.001
Waist:hip ratio	0.86 ± 15.9	0.92 ± 0.12	0.93 ± 0.13	<0.001
Systemic hypertension, %	14 (14.6)	174 (52.4)	332 (43.9)	<0.001
Diabetes, %	4 (4.2)	71 (21.4)	190 (25.1)	<0.001
Measured body fat, %	32.3 ± 9.6	33.4 ± 10.8	34.7 ± 11.5	0.11
6-minute walk distance, m	529.6 ± 97.4	354.1 ± 123.2	349.5 ± 134.4	<0.001
Laboratory				
Glucose, mg/dL	96.5 ± 17.5	106.5 ± 33.9	105.9 ± 31.9	0.025
Insulin μU/mL	9.6 [5.3–15.9]	11.6 [6.9–21.1]	9.5 [5.9–16.3]	0.005
HOMA-IR	2.3 [1.2–3.9]	2.9 [1.6–5.8]	2.4 [1.3–4.3]	0.007
Cholesterol, mg/dL	190.7 ± 39.4	173.2 ± 44.0	167.9 ± 44.5	<0.001
LDL, mg/dL	108.2 ± 32.2	93.6 ± 36.0	92.9 ± 36.1	<0.001
HDL, mg/dL	62.9 ± 20.6	54.5 ± 19.6	50.9 ± 17.0	<0.001
Triglyceride, mg/dL	98.3 ± 48.6	125.5 ± 82.7	120.5 ± 78.8	0.17
Triglyceride:HDL	1.3 [0.94–2.4]	2.1 [1.1–3.3]	2.1 [1.4–3.3]	<0.001

HOMA:IR: homeostatic model assessment of insulin resistance; m: meters.
Note: Mean ± standard deviation or median [25th percentile–75th percentile].

Table 3. Clinical and laboratory metabolic features of PH by WSPH subgroup in the PVDOMICs cohort.

	Group 1 PAH ($n = 372$)	Group 2 PH ($n = 145$)	Group 3 PH ($n = 160$)	Group 4 PH ($n = 58$)	Group 5 PH ($n = 28$)	p-value
Clinical						
Age, years	52.9 ± 14.7	67.7 ± 11.7	63.4 ± 11.0	57.3 ± 14.2	57.0 ± 13.6	<0.001
Body mass index, kg/m^2	29.0 ± 7.5	33.7 ± 9.2	29.9 ± 8.0	32.0 ± 7.4	27.8 ± 6.4	<0.001
Waist:hip ratio	0.92 ± 0.13	0.94 ± 0.11	0.93 ± 0.11	0.93 ± 0.10	1.02 ± 0.32	0.002
Systemic hypertension, %	129 (34.9)	96 (66.7)	74 (47.4)	23 (39.7)	10 (35.7)	<0.001
Diabetes, %	65 (17.6)	59 (41.0)	48 (30.8)	10 (17.2)	8 (28.6)	<0.001
Measured body fat, %	34.4 ± 11.4	38.1 ± 11.7	32.9 ± 11.6	35.3 ± 11.1	30.1 ± 10.9	0.01
Laboratory						
HOMA-IR	2.0 [1.2–3.7]	3.0 [1.8–5.4]	2.8 [1.6–4.8]	2.7 [1.3–3.8]	2.4 [1.3–3.8]	<0.001
Triglyceride:HDL	2.1 [1.3–3.5]	2.2 [1.4–3.6]	2.1 [1.5–3.1]	1.9 [1.4–3.1]	2.3 [1.5–3.2]	0.93

HOMA:IR: homeostatic model assessment of insulin resistance.
Note: Mean ± standard deviation or median [25th percentile–75th percentile].

this descriptive analysis did not attempt to address the impact of confounding and collinear relationships, nor did it examine potentially important interactions between metabolic and clinical features. It is known that insulin resistance increases with both age and BMI,[127–129] relationships that may have confounded this PVDOMICS analysis. It is not clear whether the high rates of insulin resistance observed in certain subgroups (i.e. PH and comparators vs. controls, or Groups 2 and 3 PH vs. other PH subtypes) were independent of the older age and higher BMI in these groups. Nonetheless, the data from Dr. Hemnes and colleagues reaffirm the need to further understand the role of dysregulated metabolism in PH pathogenesis. Addressing metabolic derangements could potentially improve outcomes for patients with PH. Already, therapies that target metabolic pathways are under investigation in PAH. Metformin, a biguanide, commonly used in the management of diabetes, increases fatty acid oxidation and reduces oxidant stress.[130] In a recent eight-week open-label, single-arm phase II study, 20 patients with idiopathic or heritable PAH were randomized to metformin or placebo.[131] Although a significant improvement in RV fractional area change was observed in the metformin group, the 6MWD did not improve significantly. Eight of the nine subjects who underwent magnetic resonance spectroscopy had a decrease in their RV lipid content that correlated with alterations in their plasma lipid profiles. Currently, a multicenter randomized controlled trial is recruiting to

determine the impact of metformin on a composite clinical improvement endpoint in PAH (NCT03617458).

Advancing CTEPH knowledge with a contemporary US registry

Observational PH registries offer an important snapshot of real-world data and clinician practices, permitting researchers to test hypotheses that would be impractical in controlled trial settings.[132] They have enhanced our understanding of disease epidemiology, allowing for the recognition of changing patient demographics and the identification of new risk factors. Moreover, registries have yielded insights about PAH natural history and prognosis, translating to risk assessment tools that guide treatment decisions. For other forms of PH beyond PAH (i.e. WSPH Groups 2–5 PH), dedicated registries have been less common. During the ATS virtual mini-symposium, Dr. Kim Kerr shared preliminary data from the first US Registry for CTEPH (WSPH Group 4 PH).

CTEPH involves the fibrotic transformation of pulmonary arterial thrombi with ensuing chronic vascular obstruction, distal microvascular remodeling, and eventual right ventricular failure when untreated.[133,134] The mainstay of treatment for CTEPH is PTE, a curative intervention in the majority of eligible patients.[135,136] The benefit of PTE over medical therapy has been highlighted in several single-center and international studies of European, Canadian, and Japanese patients.[136–142] An early large single-center observational CTEPH study ($n = 1500$) demonstrated that a high PVR >12.5 Wood units (WU) before PTE was associated with increased risk of 30-day mortality post-surgery. This relationship was validated in later studies.[137,138] Additional preoperative features shown to predict unfavorable surgical outcomes include WHO functional class IV heart failure symptoms, end-stage renal failure requiring dialysis, shorter 6MWD, and decompensated heart failure.[136–138] Residual post-operative pulmonary hypertension (mPAP $\geq$ 38 mm Hg and PVR > 5.6 WU) has been established as a predictor of long-term mortality risk.[143]

While this body of knowledge has helped inform the selection of appropriate PTE candidates and allowed for dynamic risk stratification, it has limitations. First, because reported observational registries have been restricted to a few geographical regions, the generalizability of their findings remains in question. Next, given that CTEPH is a rare condition (3–30 per million), sample sizes have been relatively modest. The largest registry study to date reported on only 679 subjects, encompassing 404 operated patients and 275 patients who were deemed non-operable.[138] Finally, existing studies have only compared clinical features and outcomes between operated and non-operable subjects. While this comparison has provided insights, the inherent differences in these groups that dictate operability (i.e. clot anatomy, general fitness for surgery, etc.) also introduce potential confounding biases in comparative analyses. Moreover, because registries have not yet focused on operable patients who declined surgery, what is known about the natural history of CTEPH largely stems from non-operable patients who tend to have more distal disease.

Given the aforementioned limitations, the study presented by Dr. Kerr at the ATS virtual mini-symposium is a welcome addition to the body of literature in CTEPH.[7,11] It is not only the largest and most modern CTEPH registry, but also the first to analyze the outcomes of patients who were deemed operable but did not undergo PTE.

United States CTEPH registry: Differences between operated and non-operated subjects in baseline data and one-year outcomes (presented by Kim Kerr, MD, University of California San Diego)

In this prospective observational cohort study, 750 CTEPH patients were enrolled from 30 United States centers between April 2015 and March 2018. Clinical features at baseline and at one year follow-up were reported including WHO functional class, patient-reported quality of life measures (Short Form-36 (SF-36) and EmPHasis-10 scores), hemodynamic parameters, oxygen use, diuretic use, and pulmonary vasodilator therapy. In this study, patients were classified into three groups: (1) surgical candidates who underwent PTE (operated group, $n = 565$, 75.3%), (2) non-surgical candidates (inoperable group, $n = 96$, 12.8%), and (3) surgical candidates who had operable disease but did not undergo PTE (operable/no surgery group, $n = 89$, 11.9%). Patient refusal was by far the most common reason why those in the operable/no surgery group did not undergo PTE.

Important baseline differences were found between CTEPH subgroups at study enrollment. Patients in the operated group were significantly younger (55 ± 15 years) than those in the inoperable (65 ± 13 years) and operable/no surgery group (62 ± 15 years) ($p < 0.001$). Inoperable subjects had lower BMI and were more often on background PH-directed therapy at enrollment than those in the other two groups. The operable/no surgery group had a greater proportion of Black patients and significantly better baseline quality of life measures (higher SF-36 and lower EmPHasis-10 scores) than the other two groups.

Patients who underwent PTE showed a marked hemodynamic and clinical improvement. PVR decreased from 7.9 ± 4.4 WU to 3.2 ± 2.4 WU after PTE, nearly a 60% reduction. These findings mirrored those reported an international CTEPH registry of European and Canadian patients,[138] where PTE led to a 69% PVR reduction among subjects on pulmonary vasodilator therapy and 65% reduction among those not on therapy. Interestingly, a non-trivial subset of patients in the US registry who underwent PTE (16%) were morbidly obese (BMI >40 kg/m^2).

The observed in-hospital mortality rate post-PTE was 3.8%, as compared to 4.7% in the international registry.[138]

The percentage of patients requiring PH-directed therapy in the operated group decreased from 39.5% at baseline to 22.8% at one-year post-PTE, whereas treatment rates were significantly higher at follow-up in non-PTE groups (inoperable 77.1% and operable/no surgery 60.7%, $p < 0.001$ across groups) (Fig. 7a). Clinical metrics in general improved for all subgroups from enrollment to the one-year mark, as more patients achieved WHO functional class I/II status, symptom/quality of life scores improved, and fewer subjects required oxygen and diuretic therapy (Fig. 7b–d). However, the operated group exhibited the greatest improvements and most favorable follow-up features. Remarkably, the percentage of operated patients with functional class I/II status rose from 22% pre-PTE to 83% at one year, while only 33% of inoperable and 57% of operable/no surgery patients were class I/II at follow-up ($p < 0.001$) (Fig. 7b). Similarly, at follow-up, the operated group had the best quality of life scores (Fig. 7c) and lowest rate of oxygen use (Fig. 7d). Among non-PTE groups, the operable/no surgery patients appeared to have somewhat more favorable functional class, better quality of life scores, and less oxygen use than inoperable patients

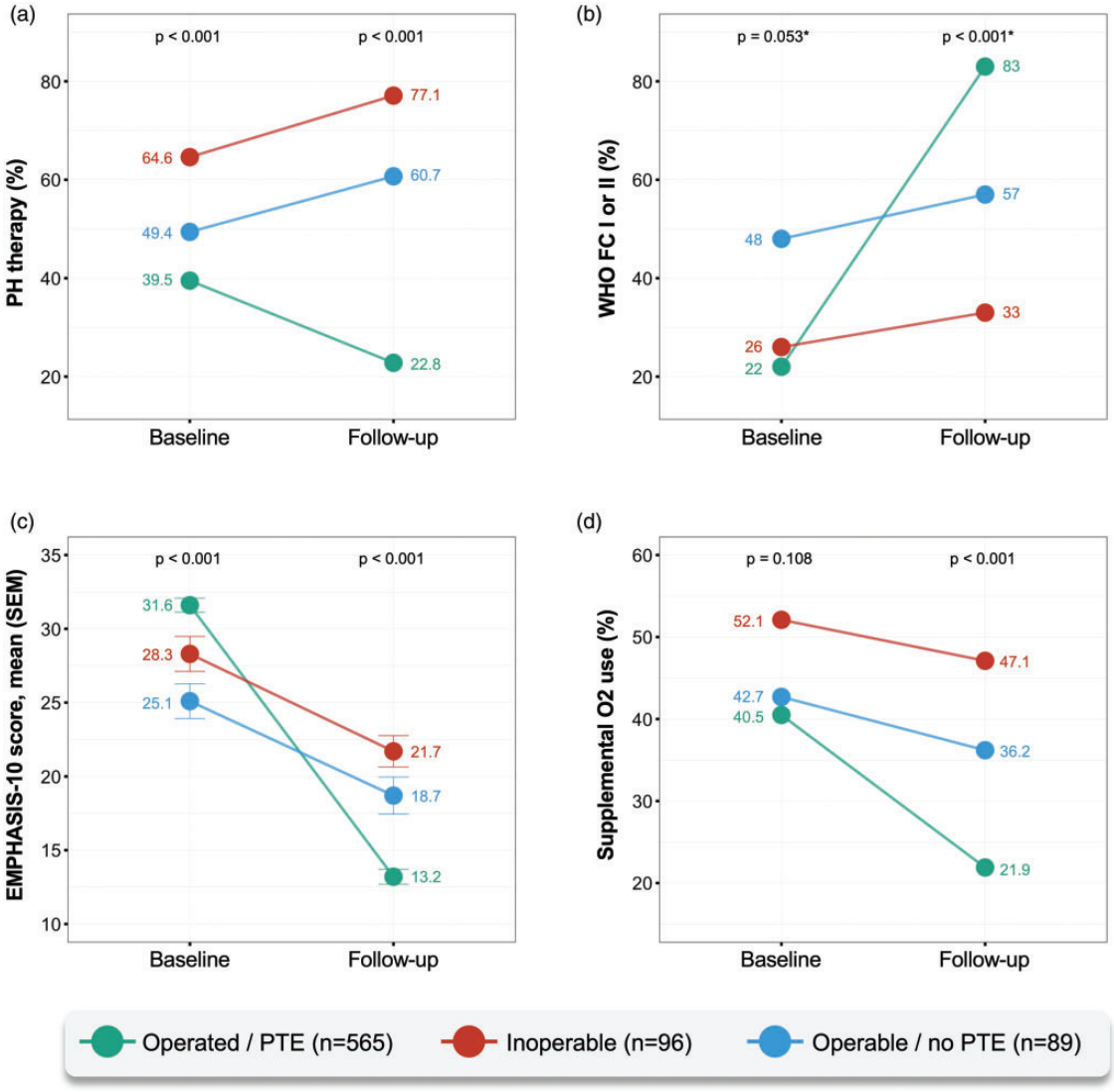

Fig. 7. United States CTEPH Registry – clinical features at baseline and at one-year follow-up by subgroup: operated (PTE) vs. inoperable vs. operable but no PTE. For each subgroup at baseline enrollment and at one-year follow-up, line plots show the (a) percentage of patients on PH-directed therapy (pulmonary vasodilators), (b) percentage of patients with WHO functional class I/II symptoms, (c) EMPHASIS-10 score (mean ± SEM), and (d) percentage of patients on supplemental oxygen. *P*-values at top of plots indicate across-subgroup comparisons at the baseline and follow-up time points (Kruskal–Wallis and Fisher's exact tests for continuous and categorical variables, respectively). PH: pulmonary hypertension; PTE: pulmonary thromboendarterectomy; SEM: standard error of the mean; O2: oxygen; WHO FC: World Health Organization functional class.

both at baseline and follow-up, yet both groups displayed similar modest improvements between time points on medical therapy.

In analysis of one-year survival, the operated group had a lower observed mortality rate than the inoperable and the operable/no surgery groups (5.5% vs. 11.5% vs. 9.0%, respectively, $p = 0.04$). These outcomes echoed those observed in a previous international registry,[138] which reported a higher one-year survival rate in operated versus non-operated subjects (93% vs. 88%, $p < 0.0001$). Dr. Kerr and colleagues concluded that PTE surgery is associated with reduced use of medical therapy, better patient-reported quality of life, and improved survival.

The strengths of this US CTEPH cohort are its large study population ($n = 750$), multicenter enrollment, racial diversity, and inclusion of an important subgroup of surgical candidates who elected to forego PTE. The authors should be commended for reporting the first large-scale observational data reflecting real-world CTEPH practices across the US. They have confirmed that PTE outcomes are favorable in the US and consistent with previously reported international data. Surprisingly, morbidly obese patients are not infrequently selected as appropriate PTE candidates (16% of operated group had BMI $>40\,kg/m^2$), and future analysis is warranted to examine outcomes in this subgroup. There is also rationale to identify predictors of peri-operative mortality risk in the US registry. Importantly, Dr. Kerr and colleagues are the first to begin characterizing the features and outcomes of operable patients who choose to forego PTE surgery. These patients had less severe symptoms and better quality of life measures at baseline than the PTE group, which likely factored into their decision against surgery. However, given the different racial distribution found in the operable/no surgery group, we speculate that cultural factors, socioeconomic status, education level, health literacy, and/or access to tertiary care may weigh into decisions surrounding PTE. Black patients with operable CTEPH underwent PTE at a disproportionately lower rate, a finding which emphasizes the need to further study and address this healthcare disparity. Although the operable/no surgery group had more favorable clinical features than the inoperable group at follow-up, this likely reflected the pre-existing differences between these groups at baseline as their clinical trajectories between time points appeared similar. Further research and long-term follow-up are needed to compare the natural history of the inoperable (i.e. more distal disease) and operable/no surgery (i.e. more proximal disease) groups. Multi-national collaboration and data sharing could help facilitate this effort.

Summary and future directions

Offering a beam of light amidst the devastating COVID-19 pandemic, this ATS virtual session brought together the PH scientific community to discuss recent work that centered on standardizing PAH diagnosis and management, improving patient risk assessment, evaluating biomarkers of disease activity, understanding metabolic dysregulation in PH, and advancing knowledge in CTEPH. The presentations not only provided a snapshot of current affairs in PH clinical research, but also afforded the chance to reflect on where the field has been and where it may be headed in the years to come.

The adult PH community has long recognized the importance of a relentless, iterative approach to updating consensus guidelines. Since experts first began convening on a regular basis to review evidence and set standards for patient care, several effective therapies have been approved for use and survival rates have improved.[144] The pediatric PH community has only recently unified to develop recommendations for patient evaluation and management, yet high quality consensus documents have emerged. Dr. Austin reviewed the updated EPPVDN consensus statement on pediatric PH, a document illustrating that a granular and informative statement is possible even when supporting evidence is relatively sparse. The EPPVDN provided new algorithms for diagnosis and treatment, an operationalized risk stratification tool, and detailed guidance on cardiac imaging modalities, genetic testing, treatment of acute PH in the ICU, and management of pediatric-specific PH subtypes. While the relative paucity of pediatric evidence required authors to base some recommendations on data extrapolated from adult studies, aspects of the EPPVDN document should also serve as an example for the adult community. For example, a forward-thinking section gave recommendations on management issues encountered in middle and low-income regions. It is acknowledged that current guidelines for adult PH are not practical in these regions,[145] but no tailored consensus recommendations have been provided. The EPPVDN's systematic approach most importantly identified knowledge gaps and clinical research priorities that will likely fuel advancements in the field (Table 4). While some of these priorities are unique to pediatric PH, the adult community is also focused on determining ideal markers of clinical severity and risk, establishing widely accepted surrogate end-points, and developing processes to improve clinical trial efficiency.

Risk stratification has become the guiding framework of consensus treatment algorithms in pediatric and adult PH, thus research efforts directed at enhancing risk prediction are unlikely to cease anytime soon. Dr. Benza introduced the virtual session audience to PHORA 2.0, a ML-based risk prediction model which appears to be the most sophisticated and accurate tool to date. The probabilistic framework of PHORA 2.0 accounts for the effects of interrelationships between multiple variables on outcome. In contrast to its predecessors which assign patients into risk strata, PHORA 2.0 provides a continuous quantitative measure of mortality risk. Given the diverse nature of the pooled international derivation cohort, the model is likely

Table 4. Clinical research priorities and future directions in pediatric PH.

Research priorities	Future directions and considerations
Identify and validate easy-to-acquire and interpret markers of clinical severity	First focus on validation of clinical parameters already included in the updated and operationalized EPPVDN risk stratification tool
Develop new treatment goals	Move beyond conventionally used targets – consider composite end-points, patient-reported outcomes, and longitudinal activity assessments (wearables)
Clinical trial process improvements	More seamlessly integrate regulatory requirements, patient recruitment, and study end-points across clinical trials
Prospective multicenter clinical trials	Prioritize studies of upfront combination therapy in moderate to severe PAH
Clearly define the role of atrial septostomy and reverse Potts shunt in advanced PH	Determine the ideal patient candidates and timing, identify contraindications
Gather data on the use, safety, and efficacy of new PH therapies in children	Promote investigator-initiated pilot and/or industry-sponsored phase 2 or 3 studies of drugs which have been recently approved for adult PH

to have generalizability in real-world populations. Although PHORA 2.0 can still yield predictions when input features are missing, the full model requires 21 clinical parameters and practicality may be an issue in some care settings. Future studies will evaluate if changes in PHORA risk with treatment are associated with outcomes. Whether the inherent strengths and predictive accuracy of this PHORA model outweigh the simplicity of other available tools will be judged as more data emerge. Ongoing advancement in the risk assessment space will depend on close international collaboration, data resource sharing, harmonization of data collection and handing processes, implementation of cutting-edge methods and technologies, and the identification of novel biomarkers that inform disease progression. Beyond the push to use risk stratification tools to guide treatment decisions, there is growing enthusiasm around employing these models to enrich clinical trial cohorts and improve the efficiency of drug development.[25]

Dr. Benza's presentation provided an elegant illustration of how machine learning can propel advancement in PH. ML has been increasingly utilized for a variety of PH research applications. Supervised ML approaches have already been applied to facilitate automated non-invasive PH diagnosis (from claims-based data,[146] cardiac imaging parameters,[147,148] and blood biomarkers[149]) prognosticate PH outcomes (from clinical and imaging features[150,151]) and predict therapy responders (from blood biomarkers[152]) Unsupervised ML has also been utilized, identifying four PAH immune phenotypes with distinct circulating inflammatory profiles that are independent of clinical subtypes and stratify mortality risk.[153] It is important to be aware of potential pitfalls as ML applications are increasingly reported in PAH. PAH is rare and ML models trained on small datasets often have poor generalizability in external cohorts, thus collaboration and data sharing will be imperative. ML is sometimes called a "dark art", as models can have limited interpretability (i.e. decision rules or key variables driving model predictions are not clear) and researcher degrees of freedom are often under-disclosed (i.e. user-defined algorithm control parameters are not reported). The success of ML efforts will depend on transparency and adherence to emerging ML reporting guidelines (i.e. the TRIPOD-ML initiative).[154] Practices that enhance model interpretability should be considered (i.e. selection of algorithms with multi-stage architecture or graphical representations to allow inspection of model decision processes, and/or post-hoc quantification of the importance of variables in the model). The capacity for ML approaches to yield useful information is also inextricably tied to dataset quality. Algorithms can be sensitive and overfit to "bad heterogeneity" (i.e. measurement or data label error, noise from background comorbidities, etc.), hence it is important for researchers to "tune" algorithm control parameters, incorporate cross-validation during model training, and test the model on real-world data. Researchers must also be aware of potential "algorithmic bias", as models can make inaccurate predictions and unfairly disadvantage certain subgroups due to inherent biases in the way training data are collected, labeled, and utilized.[155] Inclusive and representative study cohorts could provide a safeguard, and an emerging research field is focused on developing tools to detect algorithmic bias.[156] ML algorithms ultimately cannot monitor themselves for errors, and responsible human oversight will be crucial as these promising methods are applied in PH.

There is an ongoing quest in the PAH research community to evaluate non-invasive biomarkers of disease activity, as emphasized by the presentations from Drs. Peplinski and Synn. These studies of circulating Ang2 and a chest CT measure of vascular pruning exhibited how population-based cohorts of health and subclinical disease can be leveraged to provide biomarker insights. Dr. Peplinski demonstrated that increased baseline Ang2 levels were not associated with subclinical cardiac dysfunction but did predict subsequent incident heart failure. This marker, which is also associated with PAH severity and prognosis, may therefore contribute to rather than reflect the development of heart failure. Other circulating biomarkers of RV maladaptation

have also been recently reported in PAH.[55,56] Functional validation studies are warranted to elucidate the specific role of these markers in pathogenesis, as this could translate to novel RV-directed treatment targets in PAH. In another healthy population-based cohort, Dr. Synn showed that an automated CT measure of pulmonary vascular pruning, the BV5/TBV ratio, can detect early vascular remodeling that correlates with adverse changes in RV morphology and function. If further developed and validated, this marker could have implications for the screening of asymptomatic patients at risk for PAH (i.e. systemic sclerosis, BMPR2 mutation carriers) or the investigation of disease-modifying therapies in clinical trials (i.e. novel end-point for anti-proliferative agents).

Nonetheless, these biomarkers along with numerous predecessors are not ready for clinical use. Only a handful of non-invasive biomarkers have been adopted clinically to discriminate diagnosis, prognosticate, or monitor response to treatment. The PAH community stands at the crossroads with respect to biomarker research. Several circulating and imaging biomarkers have already shown promise in discovery-based observational studies, yet necessary prospective multicenter validation studies have not been conducted. Meanwhile, as high-throughput technologies advance and initiatives engaged in PH deep phenotyping emerge, the opportunity to discover more sophisticated biomarkers presents itself. International collaboration is warranted to prioritize the most promising yet practical candidate biomarkers for large-scale validation studies.

There is also a critical unmet need to identify biomarkers which predict treatment response and inform the selection of certain therapies. Available evidence does suggest this objective should be achievable. First, we have long performed acute vasodilator testing during cardiac catheterization at diagnosis to identify vasoreactive patients who respond to calcium channel blockers and have good long-term outcomes.[157,158] In secondary analysis of a large multicenter trial of sitaxsentan, relevant endothelin-1 pathway associated single-nucleotide polymorphisms were associated with differential clinical responses to the drug.[159] In a similar analysis of a recent small phase 2 randomized placebo-controlled trial of Rituximab for systemic sclerosis-associated PAH, supervised ML identified a biomarker profile (low levels of rheumatoid factor, IL-12, and IL-17) which predicted a favorable therapy response.[152] An increasing number of novel PAH therapies have failed in clinical trials despite preclinical success. Experts call for more efficient study design as a solution, and biomarker-driven strategies have been proposed to maximize knowledge gain and reduce participant risk exposure.[160,161] Biomarker-guided cohort enrichment can increase study power if biomarker-positive patients are known to benefit from treatment. Even when a biomarker is not yet an established predictor of response, biomarker-stratified or adaptive studies can inform cohort enrichment in later trial phases.[162]

Metabolic dysregulation has been recognized as a feature of PAH, ever since early preclinical and observational studies found that insulin resistance and glucose intolerance are associated with PAH and appear to contribute to disease progression.[116,118,163] Drs. Trammell and Hemnes presented observational data from two large cohorts confirming a high prevalence of metabolic abnormalities across the entire spectrum of PH. In Dr. Trammell's study of greater than 100,000 veterans, which involved a male-predominant PH cohort with a high burden of diabetes, obesity, and comorbid cardiopulmonary disease, diabetes was associated with an increased risk of death, while obesity paradoxically portended better survival. Additional research is needed to illuminate the biological mechanisms and factors that underlie this "obesity paradox" in PH. In Dr. Hemnes' study of the well-phenotyped PVDOMICs cohort, rates of metabolic abnormalities and insulin resistance were increased across all PH subtypes, including WSPH Group 1 PAH and in particular Groups 2 and 3 PH. In the future, samples collected as part of the PVDOMICs protocol will be used to conduct untargeted metabolomic profiling in the blood. Prior targeted metabolomic analyses of various tissue compartments have revealed that the metabolic dysregulation of PAH is widespread, involving alterations in glucose and fatty acid metabolism, aerobic glycolysis, and RV lipotoxicity.[119,164,165] In a recent untargeted metabolomic blood profiling study of idiopathic and heritable PAH, metabolite levels were abnormal across several bioenergetic pathways and patients with greater metabolic disturbances had worse clinical outcomes.[74] Experts have proposed metabolic dysregulation as a unifying theory of PAH pathogenesis.[166] PVDOMICs will build on available data by extending untargeted metabolomic profiling across the entire PH spectrum, including the full range of WSPH Group 1 PAH subtypes and non-Group 1 PH. Cutting-edge computational approaches, including ML and network-based approaches, will be applied to analyze and integrate these data with other -omics platforms. This work has the potential to enhance our mechanistic understanding of metabolic dysregulation in PH, may translate to the discovery of novel metabolic phenotypes, and could uncover new treatment targets.

The PVDOMICs initiative is well-positioned to yield important insights in PH beyond the metabolome, owing to its highly protocolized prospective collection of multidimensional -omics and clinical data. Other multicenter PAH biological sample and data repositories have been in existence and already led to impactful research across multiple -omics domains, including the PAH Biobank (NIH-funded US repository of Group 1 PAH patients with blood samples, www.pahbiobank.org), the Pulmonary Hypertension Breakthrough Initiative (NIH-funded US repository of tissue from the explanted lungs of idiopathic PAH

transplant recipients, www.ipahresearch.org/services), and the UK National Cohort Study of Idiopathic and Heritable PAH (www.ipahcohort.com). However, the PVDOMICs initiative is distinct given its more holistic capture of clinical phenotypic data, protocolized longitudinal profiling, and inclusion of all WSPH subgroups. Moreover, PVDOMICs is uniquely aiming to identify new disease endotypes while remaining agnostic to the current clinical classification scheme. This strategy will avoid traditional reductionist research approaches which center on specific signaling pathways or mediators, assume a common pathophenotype across patients, or anchor molecular analysis to certain clinical features/subtypes. Although patient "lumping" has contributed to significant research advancements in our field, PAH remains incurable and outcomes are overall poor with the current one-size-fits-all treatment approach. There is a role for modern research efforts focused on "splitting" to uncover disease endotypes and patient subsets that are targetable with particular therapies. Proof-of-concept was provided by the aforementioned machine learning study that identified PAH immune phenotypes with distinct blood cytokine profiles,[153] and the PVDOMICs initiative will permit this sort of agnostic molecular phenotyping approach on a multi-omics scale.

Observational multicenter clinical registries have played and will continue to play a fundamental role in advancing knowledge in WSPH Group 1 PAH, though fewer registries exist for the study of other forms of PH. Dr. Kerr presented preliminary analysis from the US CTEPH Registry, which is the largest registry of WSPH Group 4 PH to date. This work confirmed favorable PTE outcomes across a diverse US population, and follow-up data were reported from a unique subset of patients who had operable disease but elected to forego PTE. Future longer-term observation will allow the natural histories of operable and inoperable CTEPH to be compared. It may be useful for future CTEPH registries to incorporate data on balloon pulmonary angioplasty (BPA), in order to better characterize the short and long-term outcomes of this procedure. Up to 37% of patients are deemed poor surgical candidates,[167] and BPA is a viable option in some of these cases.[168,169] BPA data are largely limited to single-center studies, thus a registry-based approach to examining outcomes seems a logical next step. Future PH registries in general should be designed with a clear purpose in mind, regardless of whether the scope is Group 1 PAH, non-Group 1 PH, all forms of PH, or rare subtypes of the disease (i.e. PVOD, specific varieties of Group 5 PH, etc.). Beyond offering the potential to better understand disease incidence and prevalence, predisposing conditions, changing patient demographics, and real-world treatment practices and outcomes, these registries may isolate areas where quality improvement initiatives are needed, translate to improved approaches for disease screening and risk stratification, and identify rare but important adverse effects of treatments, among other advances.[132] The Pulmonary Hypertension Association Registry (PHAR, https://phccregistry.org/), a multicenter clinical registry of patients with Group 1 and 4 PH is an important initiative of the Pulmonary Hypertension Association-Accredited PH Care Centers (PHCC). In addition to providing insight into patient demographics, medical history, diagnostic tests, and reported quality of life over time, the data from PHAR are used to measure adherence to diagnostic and treatment guidelines, assess patient outcomes, and improve the quality of life of patients with PAH. Although most PH registries have been restricted to certain countries or geographical regions, recently launched efforts signal that large and inclusive global registries are on the horizon. The Pulmonary Vascular Research Institute (PVRI) "GoDeep Registry" aims to be the largest worldwide deep phenotyping clinical database and to offer insights into the geographical and ethnic profiles of disease (goal ~10,000 patients spanning all continents, www.pvri-godeep-registry.org). Similarly, the industry-sponsored "PHederation" initiative seeks to collate observational real-world clinical data from global PH patients to generate real-world evidence (www.phederation.org).

It is evident that strong global collaboration will be necessary to propel future clinical research advancements in PH, regardless of whether the objective is to standardize disease classification and management, improve risk stratification, identify and validate biomarkers, understand deep molecular features of pathobiology, identify new phenotypes/endotypes, build biological sample repositories, or develop observational registries. Collegial resource sharing will be imperative in the pursuit of these goals. Numerous individual PH centers and national research groups have already built comprehensive data and sample repositories, which could be thoughtfully joined to form the foundation of powerful global shared resources. Efficient and effective sharing will require consensus efforts to harmonize data collection and management processes. These data repositories should include a minimum set of core variables and impose strict data quality standards. Careful attention must be paid to geographical/international guidelines on the protection of personal data, to ensure that collaborative sharing does not threaten data privacy. When the complex multidimensional data from these collaborations are analyzed, cutting-edge informatics-based approaches must be implemented responsibly and transparently. Fortunately, global collaborations are increasingly emerging in the PH community, groups are already working to tackle the above challenges, and the future of clinical research in PH is promising.

This promising state of affairs is also exemplified by "hot off the press" PH clinical research from the 2021 ATS Conference. Multiple studies programmed in a virtual mini-symposium titled "Come Together– Clinical Advances in Pulmonary Hypertension: Lessons From Best

Abstracts" carried forward similar scientific approaches and themes to those discussed from the 2020 session, including: the application of machine learning (development of an algorithm for automated early detection of PH based on electrocardiogram features[170]) the use of contemporary PH registry data (analysis of mortality trends in the PHAR cohort[171]) the evaluation of advanced imaging-based markers of disease pathophysiology (integrated cardiac MRI and hemodynamic appraisal of right ventricular diastolic stiffness in the PVDOMICS cohort[172]) risk assessment, and the study of inoperable/not operated CTEPH (development of a risk prediction model for medically-treated CTEPH,[173] and analysis of BPA for inoperable CTEPH in an extension study of the RACE trial [174]) Furthermore, the 2021 session highlighted a study showing feasibility of a wearables-based platform for disease monitoring (remote capture of 6MWD via watch accelerometer),[175] in addition to investigations of novel therapeutic approaches (phase 2 trials of sotatercept,[176,177] and a study of Riociguat as a replacement therapy for phosphodiesterase-5 inhibitors[178]) Demonstrating a coordinated focus on addressing certain clinical research priorities, leveraging shared data resources, and applying innovative computational methods and technologies, the PH scientific community is well-positioned to advance along a path of impactful discovery.

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Conflict of interest

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