

NHLBI Workshop

Enhancing Treatments for Pulmonary Vascular Diseases (PVD) Through Precision Medicine

A Joint NHLBI-CMREF Workshop Report

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Abstract

The Division of Lung Diseases of the National Heart, Lung and Blood Institute, (NHLBI) and the Cardiovascular Medical Education and Research Fund (CMREF), held a workshop to discuss how to leverage the anticipated scientific output from the recently launched “Redefining Pulmonary Hypertension (PH) through Pulmonary Vascular Disease Phenomics” (PVDOMICS) program to develop newer approaches to pulmonary vascular disease. PVDOMICS is a collaborative, protocol driven network to analyze all PH patient populations to define novel pulmonary vascular disease (PVD) phenotypes. Stakeholders, including basic, translational and clinical investigators, clinicians, patient advocacy organizations, regulatory agencies, and pharmaceutical industry experts joined to discuss the application of precision medicine to PVD clinical trials. Recommendations were generated for research priorities in line with NHLBI Strategic Vision Goals.

1. A national effort to coordinate bio-samples and bio-data from funded programs so that information can be shared and correlated with other research projects. Example programs include PVDOMICS, PHBI, the National Biological Sample and Data Repository for PAH and the National Precision Medicine Initiative.
2. A taskforce to develop a master clinical trials protocol for PVD to apply precision medicine principles to future clinical trials. Specific features include:
 - a. Adoption of smaller clinical trials that incorporate biomarker guided enrichment strategies, using adaptive and innovative statistical designs.
 - b. Development of newer endpoints that reflect well-defined and clinically meaningful changes.

3. Development of imaging, hemodynamic, cellular, genomic and metabolic variables that will identify individual and shared features of PVD, to serve as the basis of novel phenotypes for therapeutic interventions.

Keywords: pulmonary vascular disease, pulmonary hypertension, precision medicine, master protocol, clinical trials, PVDOMICS, genomics

Introduction

For centuries doctors, scientists, and patients have known that the manifestations of a disease and its response to any particular therapy varied widely among individuals. Yet, medical practice, including pulmonary vascular disease (PVD) and pulmonary hypertension (PH), has been based upon inclusive disease definitions, with a one-size-fits-all treatment approach, despite the likelihood that multiple mechanisms of disease lead to PH (1). To change the status quo practice, several programs funded by the Division of Lung Diseases of the National Heart Lung and Blood Institute (NHLBI), have sought to subtype certain diseases based upon clinical, biochemical, and molecular biomarkers to lay the groundwork for therapies targeted to an individual's specific characteristics (2, 3). This is the promise of personalized medicine using a precision medicine approach (4).

Inadequacies of therapy of PH using the traditional approach.

From 1995 until the present, there have been 12 medicines approved for treatment of pulmonary arterial hypertension (PAH) (5). These, for the most part, have had a small impact on the outcome of the patients (6). The treatment effects on symptoms and exercise capacity are limited, with only one drug showing an improvement in survival (7). There are many reasons for the treatment failures that need to be addressed if we are to make future clinical trials for PH more successful. First, patient phenotypes are not mechanistically defined and delineated. The clinical classification of pulmonary hypertension established with the World Health Organization (WHO) in 1998 was created to enlighten physicians to the associated conditions that may affect the development or progression of pulmonary hypertension (8). In spite of the elaborate subgrouping within the clinical classification scheme, there is considerable heterogeneity and ambiguity among and within groups that makes it difficult to identify a single

group of patients who may have a common underlying pathophysiology (9). The most common form of PH today is associated with heart failure with preserved ejection fraction (HFpEF), yet there appears to be more uncertainty on how to define this group of patients than any other (10).

A second problem is the lack of satisfactory clinical trial endpoints. While the 6-minute walk (6MW) test has been the primary endpoint in most of the PAH registration trials, no minimum change has been established as a requirement (11) and (Table 1). Since walking can be affected by many physiologic variables independent of the pulmonary circulation, it becomes difficult to attribute small changes solely to a drug effect on PAH. Because PAH is usually a fatal disease, using survival as an endpoint is not practical. The recently tested “time to clinical worsening” endpoint may be useful to determine durability of a treatment effect, but it is unable to inform a physician about the efficacy of a specific therapy in a given patient (12). Additionally, there have never been endpoints that reveal the manner in which a drug is working in the pulmonary circulation in these patients. In spite of more than 20 years of therapies, there are no clear data that answer whether any of the existing medications reverse the disease, halt progression of the disease, or even affect the rate of progression of disease.

Third, there is limited understanding of the underlying mechanism of action of any treatment in human PH. Future trials need to incorporate endpoints that inform not only if a drug is effective but where it is working and how it is working, and its effect on modifying the underlying disease.

Why a precision medicine approach is appropriate for PVD.

The recent launch of the Precision Medicines Initiative (PMI) has generated interest in exploring this approach for several diseases (4). To be successful, it will require a clear understanding of the fundamental processes underlying PVD, and the identification of biological measures that will identify a specific phenotype that will predict the efficacy of a specified treatment. In actuality, a precision medicine approach is currently part of the assessment of patients with PAH. At the initial right heart catheterization of a suspected patient, vasodilator challenge is a recommended practice to determine if the patient has pulmonary vasoreactivity (13). Those who are vasoreactive can be treated with calcium channel blocker drugs, with an expectation of markedly improved clinical symptoms and up to decades of survival (14, 15). While this revelation was made years before the PMI was established, it supports the notion that identifying a highly predictive biomarker will enable effective treatment of PAH. Proof that genetic phenotyping is possible and potentially of use in treating PH also comes from the case of vasoreactive PAH. Recent work has shown that this endophenotype can be identified in the peripheral blood using RNA expression patterns (16, 17) (Figure 1) and potentially through the identification of a pattern of genetic variants (18).

PVDOMICS -Linking Phenotype with Biological Mechanisms: Seeking Precision Insights.

The 2010 NHLBI Pulmonary Vascular Strategic Plan identified the development of a comprehensive cohort to define phenotypes integrating “Omics” technologies and systems approaches as a top priority in PVD (2). The overall goal of the PVDOMICS network is to perform clinical phenotyping (demographic, physiologic, clinical chemistries, and imaging) and endophenotyping (genomic, proteomic, metabolomic, coagulomic, cell and/or tissue based) across all PH groups in order to deconstruct the traditional classification and define new

meaningful sub-classifications of patients with PVD (3). The long-term goal is utilization of endophenotypes/biomarkers for early diagnosis, at-risk screening, and personalized approaches for interventions and/or prevention of PVD. Perhaps the most innovative aspect of the analysis will be to compare all omics data without regard to PH Group designation to generate a new, more accurate classification of pulmonary vascular disease leading to PH. While it seems obvious that knowledge of the molecular mechanisms of drug effects is necessary to move the field forward, no registration clinical trial to date has included biological samples for this type of analysis. PVDOMICS seeks to explore this gap, by incorporating genetics, genomics, epigenomics, proteomics, metabolomics and coagulomics (19). (Table 1)

A genomic approach to precision medicine in PVD will be especially critical. Genetic variants are particularly well suited to apply to precision medicine because they have high specificity and thus can be measured only once. In addition, DNA is routinely extracted and can be performed on samples drawn at any time in the therapeutic intervention. RNA expression patterns, while less stable than DNA, have been validated in PAH and can be drawn in peripheral blood.

Genetic variants and gene expression patterns can be used to characterize the likelihood of a patient responding to a given drug, as illustrated by their association with clinical outcomes in patients treated with endothelin receptor antagonists (18).

The Role of Large Data Analytics.

Re-analysis of Prior Clinical Trials. One need not wait for newly defined endophenotypes to apply precision medicine strategies in PH. Clinical data from registration trials is now available to allow deeper analysis and the investigation of secondary evaluations and associations that

may not have been evident on first analysis. Randomized clinical trials have enrolled thousands of patients with PAH with detailed assessments at baseline and randomization to active therapy and placebo. Much of the data from these clinical trials are not used in the primary and secondary analyses of drug effects, and it may be difficult to study comparative effectiveness in individual studies. Yet, when harmonized in individual participant data meta-analyses, these data may be used to answer important questions in PAH, such as the response to PAH therapy by sex and race, (20) and the comparative effectiveness of treatment and risk of adverse events in distinct types of PAH such as connective tissue disease. (21, 22) A precision medicine approach, where treatments are studied in those most likely to respond, may be available by meta-analyzing multiple studies, achieving the large sample sizes often needed for such analyses.

To achieve the full potential of these completed studies and to optimize the design of future clinical trials in PAH, the creation of common data elements for PAH would facilitate both harmonization of legacy studies and start-up of future studies. Sponsors and investigators involved in the planning phase of studies should adhere to new guidelines for data sharing from the Academy of Medicine and the ICJME (23, 24).

Application of machine learning. Deep learning is a branch of machine learning that is increasing in popularity due to its ability to process highly non-linear data that requires modeling of increasingly higher level of abstractions across multiple processing layers (25, 26). Examples of uses of deep learning in medicine include automated processing and diagnosis of medical images and for making clinical predictions from large amounts of data from the electronic health record, a process that has been termed “deep patient”(27). While the current

focus on precision medicine is on –omics type data, the data that is used for machine learning can be of any type (e.g., -omics of any kind; environmental data; lifestyle data such as accelerometry; electronic health record data). Indeed for many clinical syndromes, such as PH, the genomic-centric approach may not be sufficient. PH is a complex clinical syndrome with multiple etiologies and pathophysiologies. In addition, because accessing the diseased tissue is not readily available, large-scale gene expression analyses and tissue characterization of the pulmonary vasculature are not possible. Thus, for clinical syndromes such as PH, we must leverage non-genetic data, coupled with machine learning in order to resolve the heterogeneity of the PH syndrome, which will allow for more targeted therapeutics. With improvements in phenotyping techniques, including imaging, proteomics, and metabolomics, we can take advantage of modern, “big data” analytics. For example, in patients with heart failure with preserved ejection fraction (HFpEF), a common cause of PH, the combination of deep echocardiographic phenotyping with unsupervised model-based clustering-based machine learning (i.e., “phenomapping” [Figure 2]) resulted in the detection of 3 mutually exclusive subcategories of HFpEF that differed greatly in their clinical characteristics, pathophysiology, and outcomes (28). Similar approaches could ultimately be used in PH to develop targeted, personalized therapies for specific subtypes of PH.

Considerations in the Conduct of Clinical Trials for a Precision Medicine Approach.

Primary endpoints. Early clinical trials in PAH were of short duration with the most common primary endpoint being the 6MW distance. Meta-analysis had demonstrated that change in 6MW did not correlate with other important endpoints including all cause death, hospitalization, or initiation of rescue therapy (11). Recently, time to clinical worsening has

been used as a primary endpoint in PAH trials (12) with the definition to include time to 1) all-cause mortality, 2) hospitalization for PAH, and 3) disease progression defined as worsening functional class and a reduction in 6MW. While applicable to group data, this endpoint will not be helpful for a personalized approach.

A clinical endpoint that incorporates how an individual patient feels and functions during a drug intervention is necessary for successful personalized treatments. Patient reported outcomes have not been included as primary endpoints in any of these trials. Recently, the Pulmonary Hypertension Association queried patients regarding measures of drug efficacy using a vignette describing a newly diagnosed patient with a chronic, progressive disease being prescribed a therapeutic regimen specifically for patients linked with their genetic makeup. The responses revealed that patients mostly want improvement in how they feel. Symptom reduction, increased exercise capacity and improved quality of life dominated their perceived goals, whereas improved survival, cure and reduced disease progression were about half as important. Endpoints in future clinical trials should include patient preferences as important measurements if they are to be relevant (29).

Secondary Endpoints. The clinical trials in PH have largely ignored informative endpoints essential for understanding how a drug is working in patients, and its effect on the underlying disease process. Yet, it is possible with current tools to acquire this data. These include:

- Mechanism of action. When a drug may affect vascular receptors in different circulatory beds, it would be important to ascertain on which vessels and tissues the clinical effects are manifest.

- Disease modification. Decades ago the severity of pulmonary vascular disease was estimated in patients with PAH and congenital heart disease with a simple pulmonary wedge angiogram (30) While it cannot address which cell lines are changing, it can provide an overall picture of disease progression or reversal. CT technology has now been used in a more comprehensive way in pulmonary vascular disease (31). Studies have also shown that molecular imaging of the human pulmonary vascular endothelium is possible using an adrenomedulin receptor ligand (32) (figure 3) PET scans can demonstrate increased lung 18FDG uptake in animal models and patients, and reveal changes with effective treatments (33), Figure 4.
- Right ventricular (RV) function and pulmonary vascular compliance (34). Advancing knowledge about the molecular, cellular, and functional characteristics of the RV and pulmonary arteries will accelerate progress in the treatment of PH. It is a valid strategy to develop effective therapies will be directed towards the RV, as the morbidity and mortality in PAH have been correlated best with hemodynamics and RV ejection fraction. Knowledge of whether new medications work solely on the RV, or on both the RV and pulmonary circulation is of critical importance.
- Prognostic and predictive biomarkers. The profiling of metabolites, including lipids, sugars, nucleotides, amino acids, and amines, is particularly relevant to the understanding of RV-PV dysfunction (35). The goal is to identify biomarker signatures that provide a more rational approach to clinical phenotypes, and that will predict favorable responses to each of multiple therapies (or their combination), and subsequently test resulting hypotheses in future, larger studies. Ideally it would be very

useful to establish biomarkers as surrogate endpoints in clinical trials, which could then be incorporated into adaptive trial designs (19).

Considerations in the Design of Clinical Trials.

Advances in regulatory science need to be exploited in PVD, given its orphan disease status. Several strategies have been identified which can be applied to phase II and phase III precision medicine trials (36-38). (Table 3) Predictive enrichment strategies are used to select subjects for study who have the greatest chance of benefit based on a validated biomarker. Adaptive clinical trials evaluate a treatment by measuring appropriate outcomes on a prescribed schedule, and then modify the trial protocol in a prospective strategy based on the observed effects. Modifications can be made in an adaptive manner to the dose and schedule of drug, patient selection to include enrichment with responsive patients, and avoidance of non-responders. A factorial study design allows investigators to test multiple hypotheses at once. A crossover study design has greater power compared to parallel trial design for the same number of participants. A randomized discontinuation trial is optimal for studying long-term, noncurative therapies, especially when the use of placebo is considered unethical. An N-of-1 trial design involves multiple crossover experiments performed over predefined time periods to compare the effects of different treatments on outcome measures within an individual patient. A patient enrolled in an N-of-1 trial undergoes baseline measurement of a specific outcome measure followed by an intervention for a pre-specified time period, after which performance on the outcome measures is reassessed. After a drug washout period, the same experimental design is repeated to measure the effect of a second therapy on the same outcome measures.

The Challenges

The challenge from the regulatory perspective: The development of biomarker-based approaches to personalized medicine in cardiovascular disease has been challenging, in part, because most cardiovascular therapies treat acquired syndromes which develop over many years and represent the end result of several pathophysiological mechanisms. Success in designing clinical trials for personalized medicine will require the selection of patient populations with attributes that can be targeted or that predict outcome, and the use of appropriate enrichment strategies once such attributes are identified. In oncology, the ability to identify specific molecular targets has resulted in therapies that work in small populations, but with a magnitude of benefit that is amplified. Cardiovascular studies approach hypertension and heart failure as population- based diseases and test which disease responds to specific drugs through trial and error. While there has been a long appreciation for the importance of understanding different pathways in PH, the current therapies are for all WHO PAH subgroups and work via non-pulmonary-specific vasodilation effects.

Considering the relatively modest benefits that PAH drugs possess, regulatory agencies have tolerated considerable uncertainties in the safety profile resulting from much smaller safety databases than are typically expected of chronic therapies. This uncertainty will be aggravated by further reduction in the size of development programs targeting progressively more constrained populations. This means that the benefits with such targeted therapies will need to be fundamentally larger than those of current drugs, e.g. mortality, avoidance of hospitalization, or functional or symptomatic improvements unequivocally large enough for individual subjects to

perceive as meaningful. More reliance on post marketing surveillance of efficacy and safety will be inevitable.

The FDA has permitted the use of drugs that have a proven benefit on some disease marker, even if that marker is not wholly satisfactory to the field. In PAH, the 6 MW is an example. If a drug has a satisfactory safety profile and gives a statistical increase in the 6MW, the drug is approvable. If post-marketing use of the drug identifies a significant toxicity the FDA has the responsibility and right to either demand a boxed warning, or to decertify a drug from the marketplace. The FDA is poised to be a partner in the evolution of precision medicine based on better understanding of shared mechanisms of disease in PH cohorts, and will work with trialists and the pharmaceutical industry to develop satisfactory trial designs and to aid in innovative approaches towards PH, Figure 6.

Pharmaceutical industry challenges with precision medicine clinical trials.

The advances in genomics, and understanding of individual responses to efficacy and safety of therapeutics has challenged the traditional “one size fits all” drug development paradigm. As the cost of drug development has accelerated, with the average cost for one new approved drug a staggering \$2.6B (2000 – 2010), the industry is looking for more efficient drug development pathways. While the overall likelihood of regulatory approval from phase 1 for all drug candidates is approximately 10%, the success rate increases with use of selection biomarkers and in rare diseases. New drugs for PVD will require new models of collaboration between academia, industry and the FDA. These consortia must address the organizational complexity to gain the potential benefits. These include the sharing and/or combination of biomarker databases, agreement on intellectual property rights, standardization of operating

procedures in a clinical consortium, decisions on funding and influence within a consortium, and how prioritization and other decisions are made. Industry needs to be open minded as to what constitutes a true commercial advantage which must be protected yet maintaining the spirit of open collaboration and most important, the interests of the patients.

Clinical trials in PAH have many challenges. The sample sizes required to establish the utility of novel drugs and therapeutics is increasing for reasons that include the paucity of treatment naïve patients, and the small incremental improvements anticipated in traditional endpoints that necessitate high enrollment numbers for adequate powering. Heterogeneity of treatment effects is a problematic issue. Specifically, those that benefit most from novel treatments are usually the most severely affected by PAH, but small in number. Conversely, the least severely affected which are available to study are those that receive little benefit from the treatments. However, these less ill patients are exposed to same risks for side effects as the most severely affected people. In addition, the least severely affected PAH patients also have the least room for improvement in response to effective novel treatment, leading to increased clinical trial sample sizes.

The cost of new medicines will continue to draw attention, as niche drugs usually come with high price tags. Political tensions will probably increase when patients are denied access to precision medicines for financial reasons. The FDA is not in a position to intercede in this area, but societal demands will require a dialogue between the payers and the drug sponsors.

Summary of Recommendations to the National Heart, Lung and Blood Institute

1. A national effort, led by the NIH, should seek to co-ordinate bio-samples and bio-data from all funded programs to a web based repository so that information can be shared and correlated with other and all research projects. This should be a requirement of all future multicenter trials.
2. Genomic data should be coordinated with the National Precision Medicine Initiative so that large genetic databases can be used to detect genotype-phenotype relationships.
3. A taskforce, inclusive of the principle stakeholders, should be created to develop a Master Clinical Trials Protocol for PVD that will apply precision medicine principles to future interventional clinical trials. With the input and approval of regulatory agencies, the Master Protocol would provide a reasonable path for drug development (Phase II) and registration (Phase III), while it addresses the needs of academia, clinicians and patients. Specifically:
 - Patient centered outcome measures that incorporate patient needs and preferences should be identified in PVD, and included, in future clinical trials along with traditional medical outcomes measures.
 - As the development of precision medicine initiatives alter the size and composition of clinical trials, statistical expertise and FDA insights will be needed to allow for flexible and innovative statistical design.
 - There is a need for testing of newer endpoints, both primary and secondary, that represent well-defined and clinically meaningful changes which accurately reflect whether a drug is working in a given patient.

- There should be ongoing development of static and dynamic imaging, hemodynamic, cellular, genomic and metabolic variables that will identify patients for their personal features. Such development should be hypothesis based where possible to reveal differences that can lead to improved trials development whose effects can be objectively measured.

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References:

1. Tudor RM, Archer SL, Dorfmueller P, Erzurum SC, Guignabert C, Michelakis E, Rabinovitch M, Schermuly R, Stenmark KR, Morrell NW. Relevant Issues in the Pathology and Pathobiology of Pulmonary Hypertension. *J Am Coll Cardiol* 2013; 62: Supplement D4-12.
2. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM. National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010; 181:315–323.
3. NHLBI and CMREF Workshop on Enhancing Treatments for Pulmonary Vascular Diseases (PVD) Through Precision Medicine. Meeting Date(s): June 6- June 7, 2016. *Home » Health Information for the Public » Resources for the Public » Lung Diseases » NHLBI and CMREF Workshop On Enhancing Treatments for Pulmonary Vascular Diseases (PVD) Through Precision Medicine.*

4. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015; 372(9):793-
PMID: 25635347
5. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of Pulmonary Arterial Hypertension. *J Am Coll Cardiol* 2015; 65(18):1976-1997.
6. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaïci A, Weitzenblum E, Cordier, J-F, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jaïs X, Montani D, Souza R, Simonneau G. Survival in Patients With Idiopathic, Familial, and Anorexigen-Associated Pulmonary Arterial Hypertension in the Modern Management Era. *Circulation* 2010; 122:156-163.
7. Macchia A, Marchioli R, Tognoni G, Scarano M, Marfisi RM, Tavazzi L, Rich S. Systematic review of trials using vasodilators in pulmonary arterial hypertension: why a new approach is needed. *Am Heart J* 2009; 159: 245-257.
8. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrec D, Speich R, Beghetti M, Rich S, Fishman. A clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004 Jun 16; 43(12 Suppl S):5S-12S.
9. Ghofrani HA, Wilkins MW, Rich S. Uncertainties in the diagnosis and treatment of pulmonary hypertension. *Circulation* 2008; 118: 1195-1201.
10. Borlaug BA. Invasive Assessment of Pulmonary Hypertension: Time for a More Fluid Approach? *Circ Heart Fail* 2014; 7:2-4.

11. Savarese, G., et al., Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? a meta-analysis of 22 randomized trials. *J Am Coll Cardiol* 2012; 60(13): 1192-201.
12. McLaughlin, V.V., et al., End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54(1 Suppl): p. S97-107.
13. Hoeper M, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB, Definitions and Diagnosis of Pulmonary Hypertension. *J Am Coll Cardiol* 2013; 62(25S).
14. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987; 76: 135-141.
15. Sitbon O, Humbert M, Jais X, Loos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111: 3105-3111.
16. Hemnes AR, Trammell AW, Archer SL, Rich S, Yu C, Nian H, Penner N, Funke M, Wheeler L, Robbins IM, Austin ED, Newman JH, West J. Peripheral blood signature of vasodilator-responsive pulmonary arterial hypertension. *Circulation* 2015; 131: 401-409.
17. Hemnes AR, Zhao M, West J, Newman JH, Rich S, Archer SL, Robbins IM, Blackwell TS, Cogan J, Loyd JE, Zhao Z, Gaskill C, Jetter C, Kropski JA, Majka SM, Austin ED. Critical Genomic Networks and Vasoreactive Variants in Idiopathic Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med* 2016; 194(4):464-75.

18. Benza RL, Gomberg-Maitland M, Demarco T, Frost AE, Torbicki A, Langleben D, Pulido T, Correa-Jaque P, Passineau MJ, Wiener HW, Tamari M, Hirota T, Kubo M, Tiwari HK. Endothelin-1 Pathway Polymorphisms and Outcomes in Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med* 2015; 192: 1345-1354.
19. PVDOMICS protocol to be available soon on web.
20. Gabler NB, French B, Strom BL, Liu Z, Palevsky HI, Taichman DB, Kawut SM, Halpern SD. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. *Chest* 2012; 141:20-6.
21. Rhee RL, Gabler NB, Praestgaard A, Merkel PA, Kawut SM. Adverse Events in Connective Tissue Disease-Associated Pulmonary Arterial Hypertension. *Arthritis & Rheumatology* 2015; 67:2457-65.
22. Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM. Comparison of Treatment Response in Idiopathic and Connective Tissue Disease-associated Pulmonary Arterial Hypertension. *Am J Resp Crit Care Med* 2015; 192:1111-7.
23. Institute of Medicine (U.S.). Committee on Strategies for Responsible Sharing of Clinical Trial Data, Institute of Medicine (U.S.). Board on Health Sciences Policy. Sharing clinical trial data: maximizing benefits, minimizing risk. *National Academy of Sciences* 2015.
24. Taichman DB, Backus J, Baethge C, Bauchner H, de Leeuw PW, Drazen JM, Fletcher J, Frizelle FA, Groves T, Haileamlak A, James A, Laine C, Peiperl L, Pinborg A, Sahni P, Wu S. Sharing Clinical Trial Data--A Proposal from the International Committee of Medical Journal Editors. *The N Engl J Med* 2016; 374:384-6.
25. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015; 521:436-444.

26. Chan SY and Loscalzo J. The emerging paradigm of network medicine in the study of human disease. *Circ Res* 2012; 111:359-74.
27. Miotto R, Li L, Kidd BA, Dudley JT. Deep Patient: An Unsupervised Representation to Predict the Future of Patients from the Electronic Health Records. *Sci Rep* 2016; 6:26094.
28. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, Bonow RO, Huang C-C, Deo RC. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation* 2015; 131:269-279.
29. Peacock AJ, Naeije R, Galiè N, Rubin L. End-points and clinical trial design in pulmonary arterial hypertension: have we made progress? *Eur Respir J* 2009 Jul; 34(1):231-42.
30. Rabinovitch M, Keane JF, Fellows KE, Castaneda AR, and Reid L. Quantitative analysis of the pulmonary wedge angiogram in congenital heart defects. Correlation with hemodynamic data and morphometric findings in lung biopsy tissue. *Circulation* 1981; 63:152-164.
31. Lau EMT, Manes A, Celermajer DS, Galiè N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. *European Heart J* 32:20; 2489 – 2491.
32. Létourneau M, Nguyen QT, Harel F, Fournier A, Dupuis J. PulmoBind, an Adrenomedullin-Based Molecular Lung Imaging Tool. *J Nucl Med* 2013; 54:10 (1789-1796).
33. Zhao L, Ashek A, Wang L, Fang W, Dabral S, Dubois O, Cupitt J, Pullamsetti SS, Cotroneo E, Jones H, Tomasi G, Nguyen Q, Aboagye EO, El-Bahrawy MA, Barnes G, Howard LS, Gibbs JSR, Gsell W, He J-G, Wilkins MR. Heterogeneity in Lung 18FDG Uptake in Pulmonary Arterial Hypertension Potential of Dynamic 18FDG Positron Emission Tomography With Kinetic Analysis as a Bridging

Biomarker for Pulmonary Vascular Remodeling Targeted Treatments. *Circulation* 2013; 128:1214-1224.

34. van de Veerdonk MC, Kind T, Marcus JT, Mauritz G-J, Heymans MW, Bogaard H-J, Boonstra A, Marques KMJ, Westerhof N, Vonk-Noordegraaf A. Progressive Right Ventricular Dysfunction in Patients With Pulmonary Arterial Hypertension Responding to Therapy. *J Am Coll Cardiol* 2011; 58(24):2511-2519.

35. Talati M, Hemnes A. Fatty acid metabolism in pulmonary arterial hypertension: role in right ventricular dysfunction and hypertrophy. *Pulm Circ* 2015; 5(2): 269–278.

36. Grieve AP¹, Chow SC, Curram J, Dawe S, Harnisch LO, Henig NR, Hung HM, Ivy DD, Kawut SM, Rahbar MH, Xiao S, Wilkins MR. Advancing clinical trial design in pulmonary hypertension. *Pulm Circ* 2013; 3(1):217-25.

37. Lythgoe MP, Rhodes CJ, Ghataorhe P, Attard M, Wharton J, Wilkins MR. Why drugs fail in clinical trials in pulmonary arterial hypertension, and strategies to succeed in the future. *Pharmacol Ther* 2016; S0163-7258(16)30058-4.

38. Wholley D. The Biomarkers Consortium. *Nat. Rev. Drug. Discov.* 2014; 13:791-792.

39. Printz, C. I-SPY 2 may change how clinical trials are conducted. *Cancer* 2013; 119 (11): 1925–27.

40. Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER) February 2010 www.fda.gov/downloads/Drugs/.../Guidances/ucm201790

41. Blumenschein G, Saintigny P, Liu S, Kim E, Tsao A, Herbst R, Alden C, Lee J. Comprehensive biomarker analysis and final efficacy results of sorafenib in the BATTLE Trial. *Clinical Cancer Research* 2013; 24:6967-75.
42. http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014.
43. Rich S. The six minute walk test as a primary endpoint in clinical trials for pulmonary hypertension. *J Am Coll Cardiol*. 2012; 60: 1202-1203.
44. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 2006; 114:1482-1489.

Table 1. The reported change in 6 minute walk distance in patients randomized to active therapy in the PAH registration trials. Courtesy of Valerie McLaughlin and Robert Frantz.

Drug	Change in walk (meters)
epoprostenol i.v.	31
bosentan	36
ambrisentan	45
macitentan	12
sildenafil	45
tadalafil	33
riociguat	30
iloprost (inhaled)	18
treprostinil (s.q.)	10
treprostinil (i.v.)	not measured
treprostinil (inhaled)	14
treprostinil (oral)	13
selexipag	4

i.v.= intravenous. s.q.=subcutaneous

Comparisons between drugs should not be made from these results, as the trials varied with respect to the severity of the PAH, and the use of background therapies. The minimal improvement for a patient to acknowledge a real benefit has been reported to between 54 and

80 meters. (43) Exercise training in patients who are stable on optimal therapy can increase their 6MW distance by 96 meters. (44)

Table 2. Genomic, epigenomic, proteomic, metabolomic and coagulomic biomarkers with potential application to a precision medicine approach to PVD (19)

- endothelial and smooth muscle cell biology with:
 - BMPR2
 - KCNK3 (and other ion channels)
 - endothelin
 - angiotensin
 - serotonin mediator networks and
 - circulating progenitor cells that mark injury and repair processes
- hypoxia signaling pathways
- coagulation:
 - initiation of coagulation (procoagulant activity),
 - coagulation cascade,
 - fibrinolysis
- markers of heart health
 - BNP / ANP peptides; troponin), braveheart RNA
- function of hormone receptor signaling (e.g. estrogen receptor, aldosterone receptor)
- cancer-like processes
- arachidonic acid signaling network

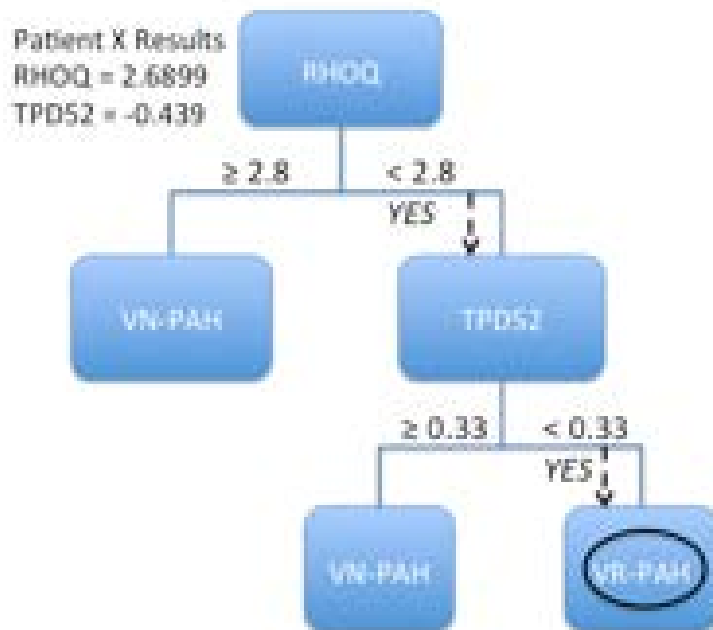
- determinants of nitric oxide and guanylyl cyclase signaling
- metabolic shift in lung, vascular, heart and immune cells with mitochondrial remodeling;
 - metabolic syndrome,
 - insulin resistance and
 - type II diabetes
- matrix remodeling of the lungs, the pulmonary blood vessels and the heart
 - proteases to anti-protease imbalance;
 - fibrosis
- oxidative stress in the cell environment and intracellular imbalance of the redox system
- responses by the network hubs of
 - Interleukin (IL)– 1
 - Tumor necrosis factor – TNF super-families.
- immune response mediators
 - network hubs of IL-13 / IL-4 including resistin like molecule
 - the IL-33 receptor ST2
 - IL-17A
 - IL-6
- Interferon response
 - network hubs of type-I Interferons (IFN) and IFN γ)

Table 3. Characteristics of Proposed and Established Study Designs in PAH

Trial Type	Design	Advantage	Limitation
Randomized controlled trial	Patients randomized to study agent or placebo and outcomes assessed at follow-up	Placebo control demonstrates efficacy. Powered adequately to determine effect	Expense Ethics of placebo use Subpopulations not well studied
Factorial design	≥2 factors, each with ≥2 levels: 2×2 factorial design; drug A+placebo B; placebo A+placebo B; placebo A+active B; active A+active B	Test multiple hypotheses at once Test combination of agents	Potential interaction between agents
Crossover study	Each subject is administered a particular therapy at different time points	Within-subject analysis possible Smaller sample size necessary	Rapid clinical deterioration may affect results and limit eligibility of patients
Randomized discontinuation trial	Responders to drug therapy are randomly assigned to placebo or continued treatment	Removal of patients who are therapy nonresponders is an element of study design	Adverse events may occur on withdrawal of drug
N-of-1 clinical trial	Multiple crossover experiments over a predefined time period	Individualized therapeutic response identified.	Limited statistical power, generalizability of findings to other patients unknown

Adapted with permission from: Ryan JJ, Rich JD, Maron BA., MD. Building the Case for Novel Clinical Trials in Pulmonary Arterial Hypertension. Circ Cardiovasc Qual Outcomes. 2015; 8: 114-123

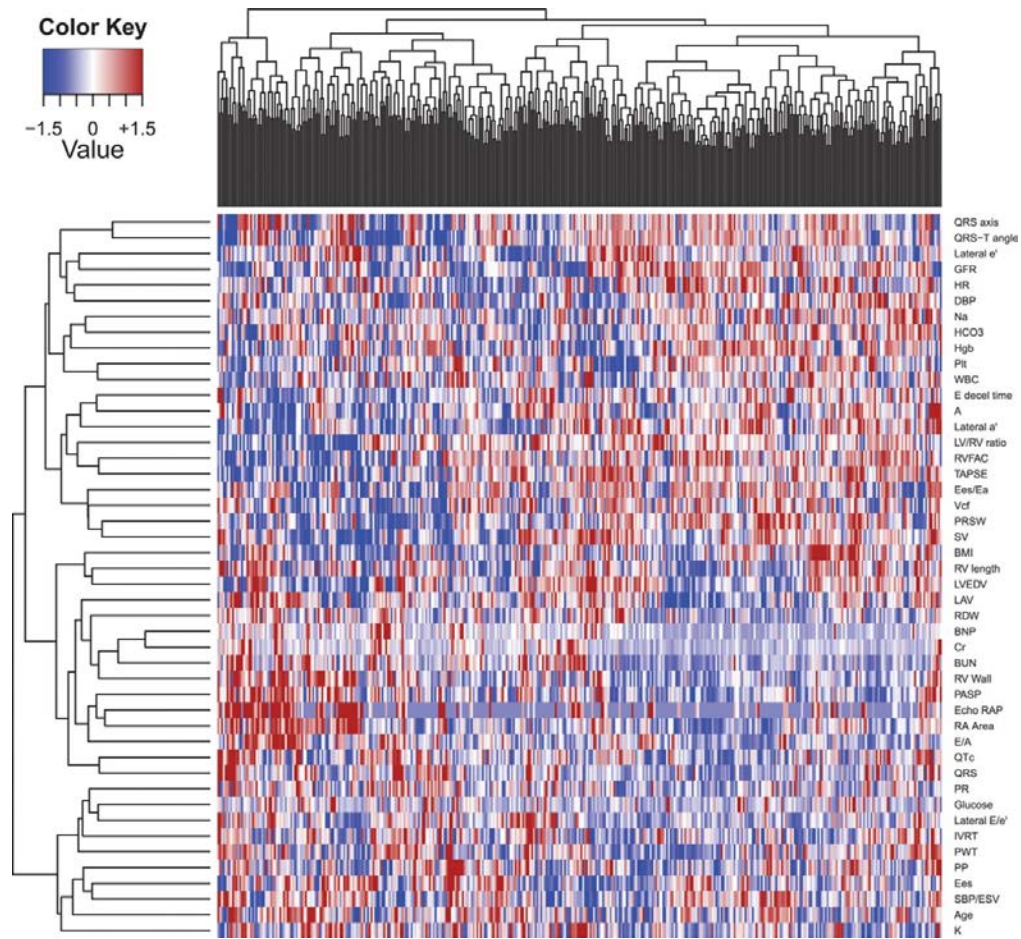
Figure 1. Example of a decision tree to differentiate vasodilator responsive pulmonary arterial hypertension (VR-PAH) from vasodilator-nonresponsive pulmonary arterial hypertension (VN-PAH).



Adapted with permission from: Hemnes AR, Trammell AW, Archer SL, RICH S, Yu C, Nian H, Penner N, Funke M, Wheeler L, Robbins IM, Austin ED, Newman JH, West J. Peripheral blood signature of vasodilator-responsive pulmonary arterial hypertension. *Circulation* 2015; 131: 401-409.

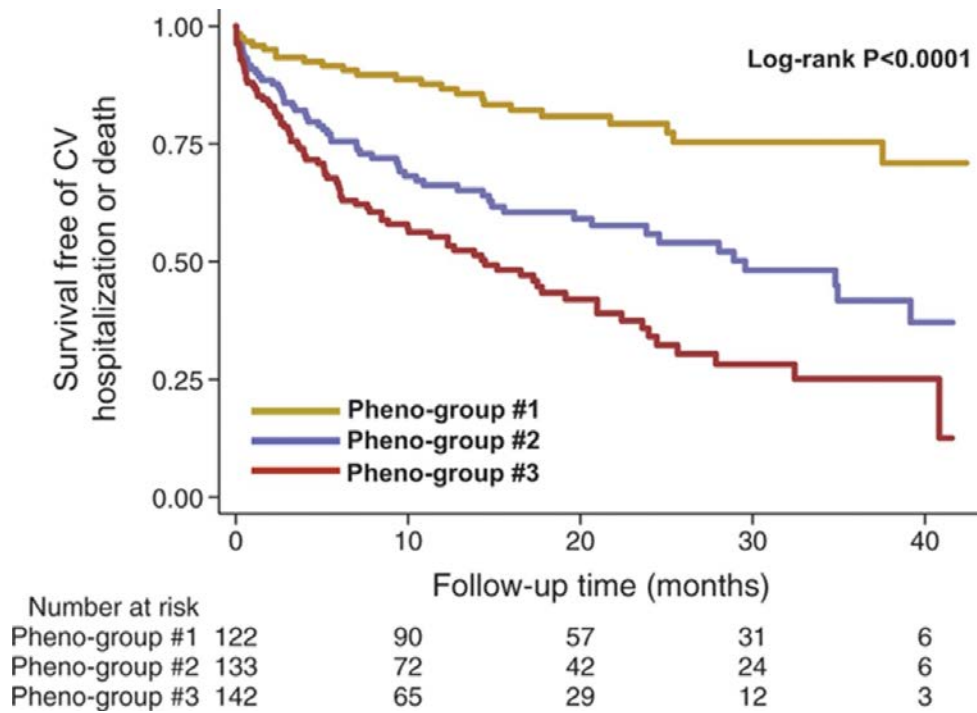
Figure 2: Phenomapping for novel classification of heart failure with preserved ejection fraction.

A. Phenotype heat map (phenomap) of heart failure with preserved ejection fraction



Columns represent individual study participants; rows, individual phenotypes. Red indicates increased value of a phenotype; blue, decreased value of a phenotype.

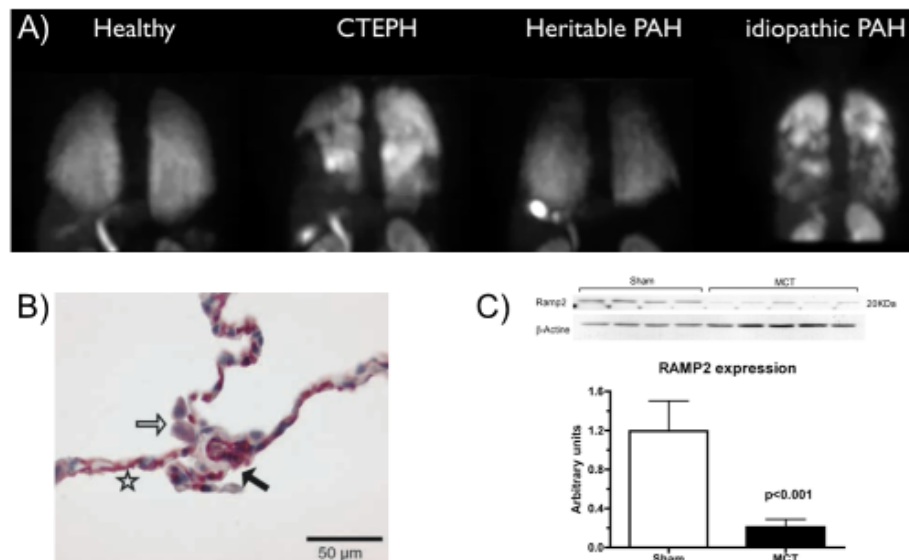
A. Survival free of cardiovascular (CV) hospitalization or death stratified by phenogroup



Adapted with permission from: Sanjiv J. Shah, Daniel H. Katz, Senthil Selvaraj, Michael A. Burke, Clyde W. Yancy, Mihai Gheorghiade, Robert O. Bonow, Chiang-Ching Huang and Rahul C. Deo. Phenomapping for Novel Classification of Heart Failure with Preserved Ejection Fraction. *Circulation*. 2015; 131:269-279

Figure 3. Selective Adrenomedullin Receptor Ligand as an Imaging Modality of the Pulmonary Vascular Endothelium

A) Molecular SPECT imaging of the pulmonary circulation with ^{99m}Tc -PulmoBind, a selective adrenomedullin receptor ligand, in a healthy human and in subjects with PH. B) Intense staining (red) of the adrenomedullin receptor in human lung capillaries. C) Reduced protein expression of the adrenomedullin receptor in the rat monocrotaline model of PH.

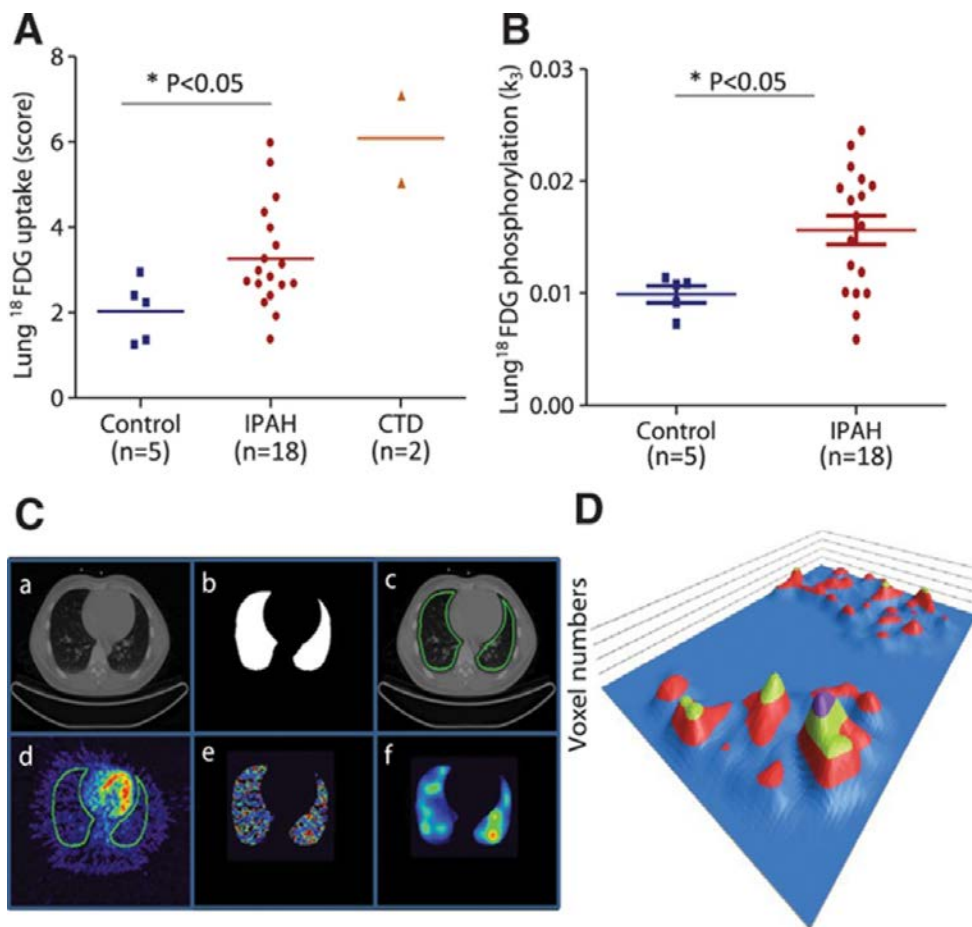


Adapted with permission from:

1. Hagner S, Stahl U, Knoblauch B, McGregor GP, Lang RE. Calcitonin receptor-like receptor: Identification and distribution in human peripheral tissues. *Cell Tissue Res.* 2002;310:41-50
2. Dupuis J, Harel F, Fu Y, Nguyen QT, Letourneau M, Prefontaine A, Fournier A. Molecular imaging of monocrotaline-induced pulmonary vascular disease with radiolabeled linear adrenomedullin. *J Nucl Med.* 2009;50:1110-1115

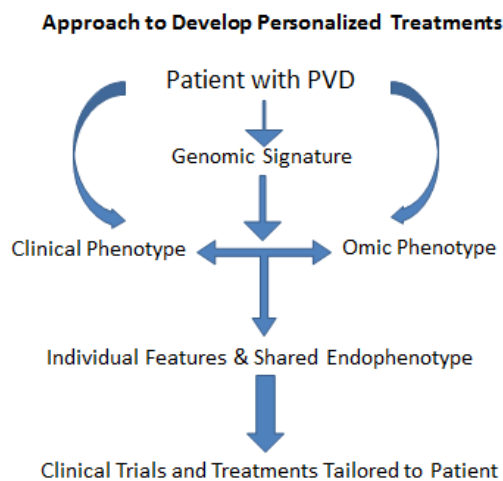
Figure 4. Lung FDG uptake in patients with PAH are shown in comparison to normal control patients.

A, ^{18}F FDG uptake in the IPAH patient group was increased compared with controls. **B**, Two-tissue compartment model analysis demonstrated a significantly higher k_3 in IPAH patient lungs than in control subjects consistent with increased intracellular glucose metabolism. **C**, **a**, Computed tomographic thorax image (transverse view). **b**, Computed tomographic thresholding to define lungs. **c**, Defined region of interest in computed tomographic view of lung parenchyma. **d**, Coregistration of region of interest with positron emission tomography image. **e**, Representative map of lung parametric FDG score in region of interest. **f**, Distribution of voxels with top 25% FDG scores in region of interest. **D**, Representative 3-dimensional parametric map generated from computed per-voxel FDG scores from an IPAH patient showing uneven FDG uptake within the lung.



Adapted with permission from: Lan Zhao, Ali Ashek, Lei Wang, Wei Fang, Swati Dabral, Olivier Dubois, John Cupitt, Soni Savai Pullamsetti, Emanuele Cotroneo, Hazel Jones, Gianpaolo Tomasi, Quang-De Nguyen, Eric O. Aboagye, Mona A. El-Bahrawy, Gareth Barnes, Luke S. Howard, J. Simon R. Gibbs, Willy Gsell, Jian-Guo He and Martin R. Wilkins. Heterogeneity in Lung 18FDG Uptake in Pulmonary Arterial Hypertension. Potential of Dynamic 18FDG Positron Emission Tomography with Kinetic Analysis as a Bridging Biomarker for Pulmonary Vascular Remodeling Targeted Treatments. *Circulation*. 2013; 128:1214-1224

Figure 6



Schematic approach to acquire basic and phenotypic information on multiple individuals and groups of patients with pulmonary vascular disease (PVD). This information will lead to therapies and trials that are more directed at specific mechanisms of disease than is now possible.

