

PVDOMICS

Study Introduction

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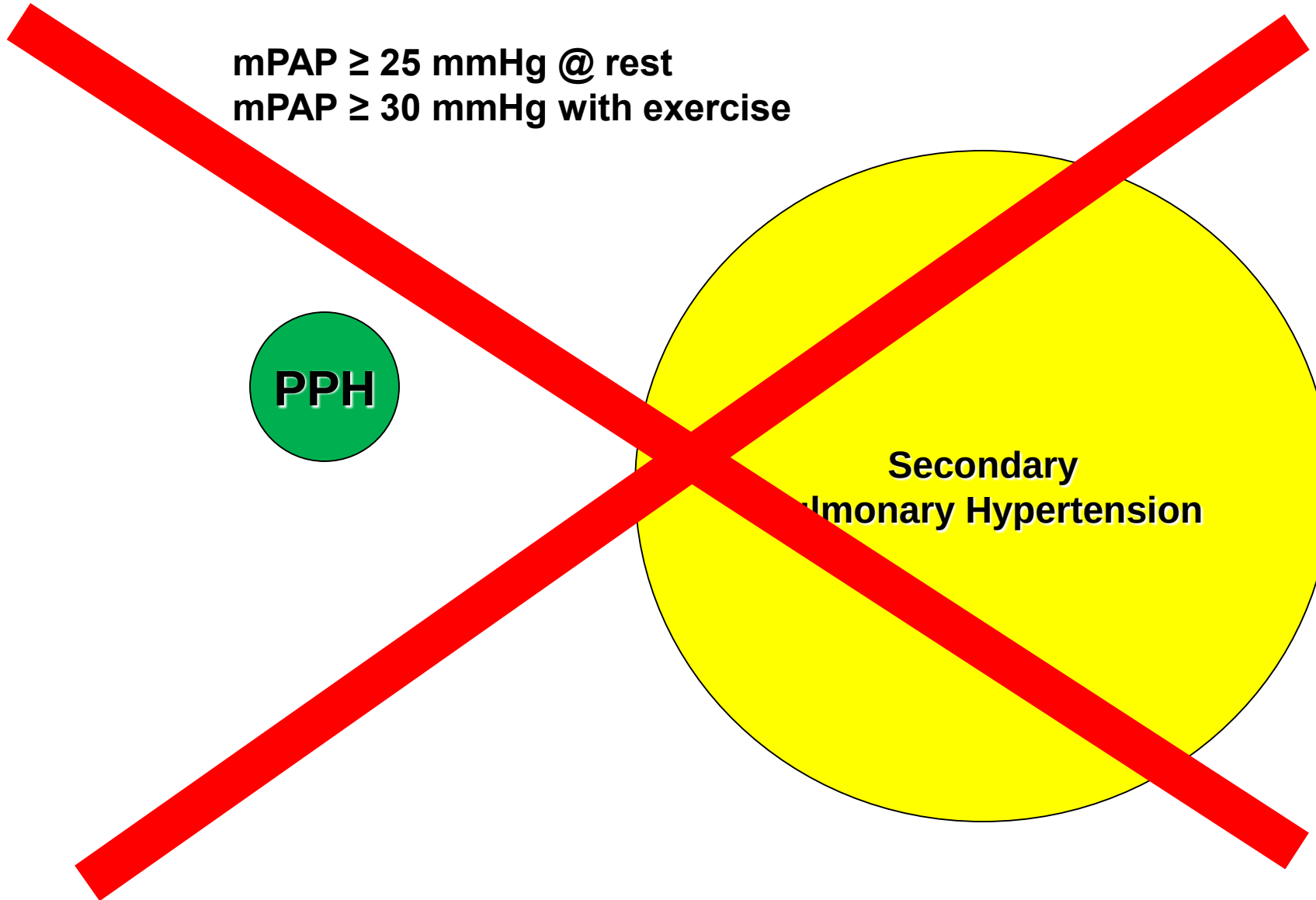
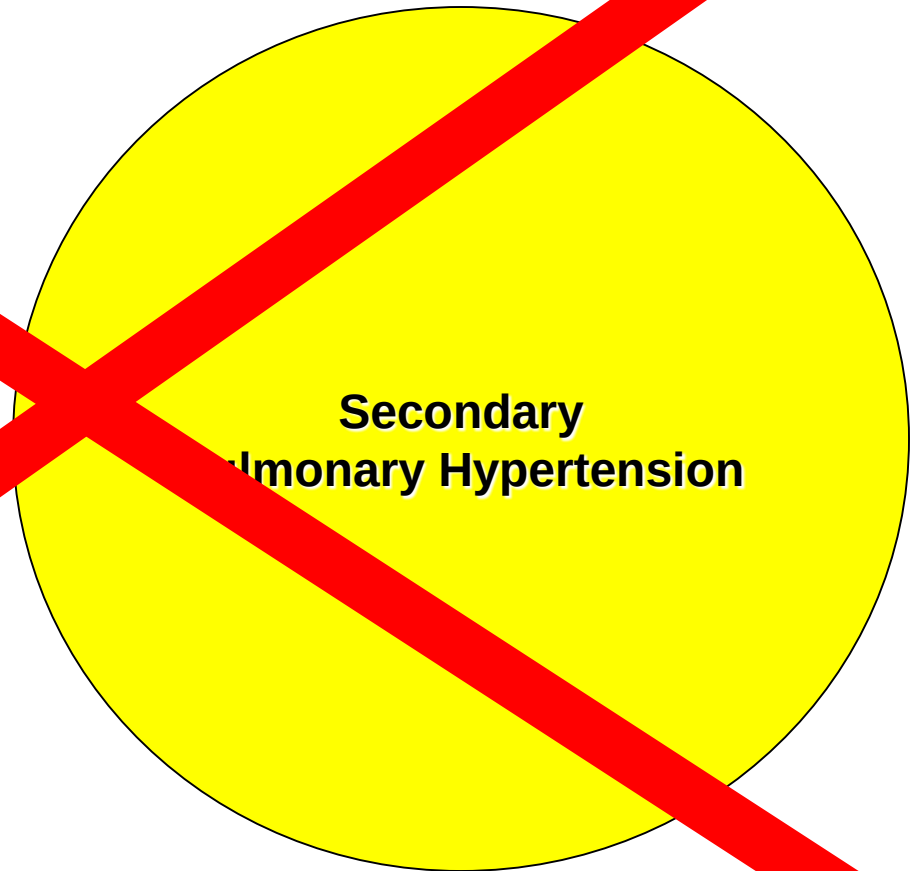


NHLBI Pulmonary Vascular Disease Phenomics Program

*Funded by the National Heart, Lung, and Blood Institute of the
National Institutes of Health with support from
the Pulmonary Hypertension Association*

The Way It Was...

mPAP $\geq$ 25 mmHg @ rest
mPAP $\geq$ 30 mmHg with exercise





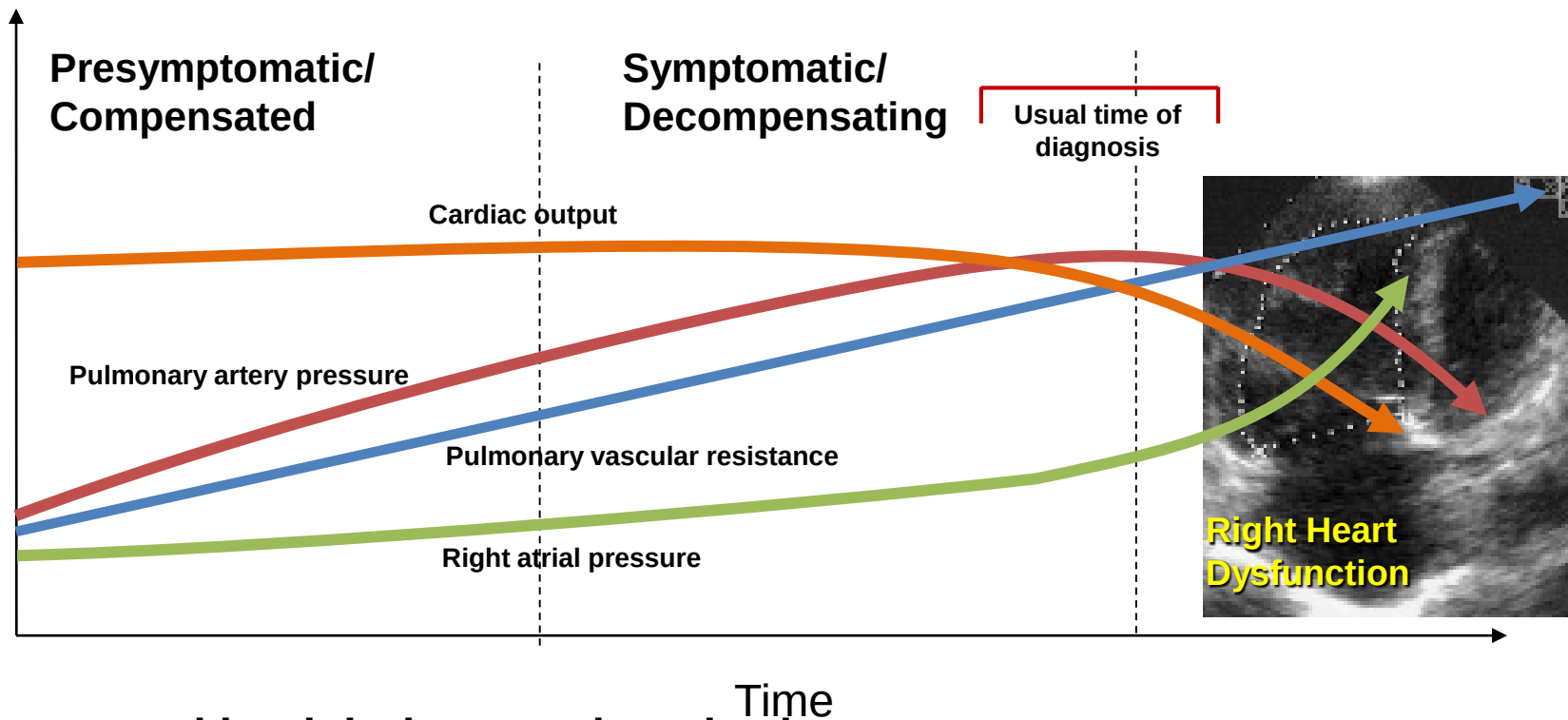
5th World Symposium on Pulmonary Hypertension

Diagnostic Definition of PH

Pulmonary Hypertension

Mean pulmonary artery pressure (mPAP)

≥25 mm Hg



As measured by right-heart catheterization.

Adapted from: Hill NS. *Pulmonary Hypertension Therapy*. Summit Communications, LLC; 2006:9.

Hoeper MM, et al. *J Am Coll Cardiol*. 2013;62:D42-50.

5th World Symposium on Pulmonary Hypertension

Diagnostic Definition of PAH

Pulmonary Arterial Hypertension (PAH)

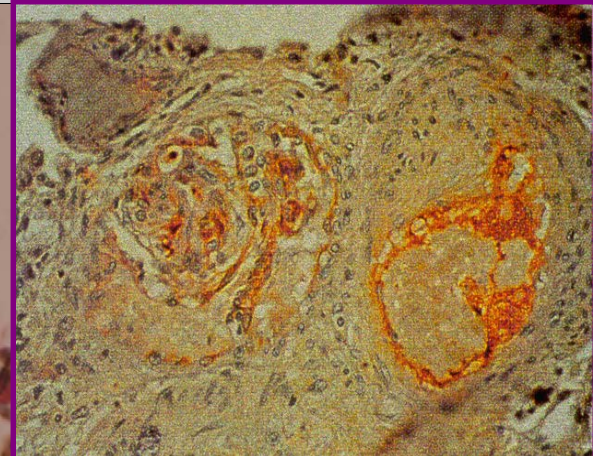
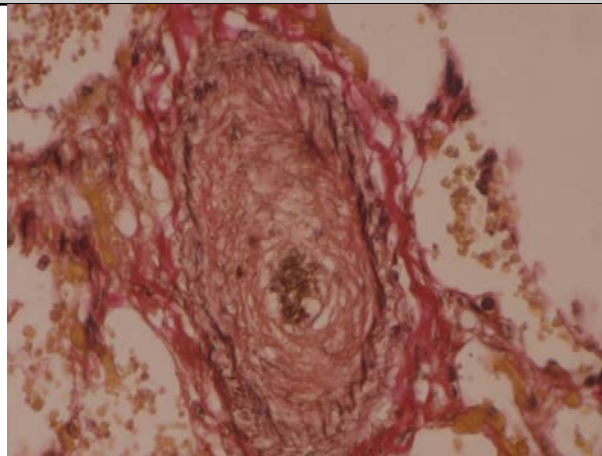
Mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg

And

Mean pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg

With

Pulmonary vascular resistance (PVR) > 3 Wood units



5th WSPH: Classification of Pulmonary Arterial Hypertension by Etiology

1. Pulmonary arterial hypertension

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
 - 1.2.1 BMPR2
 - 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
 - 1.2.3 Unknown
- 1.3 Drug-and toxin-induced
- 1.4 Associated with
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
- 1'' Persistent pulmonary hypertension of the newborn

2. PH due to left heart disease

- 2.1 LV systolic dysfunction
- 2.2 LV diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital/acquired left heart inflow/outflow obstruction

3. PH due to lung disease and/or hypoxia

- 3.1 COPD
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension

5. PH with unclear multifactorial mechanisms

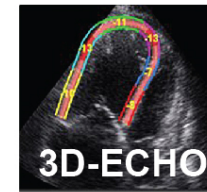
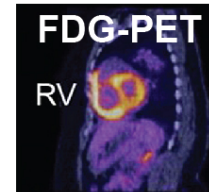
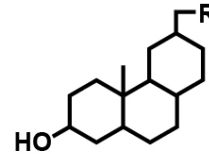
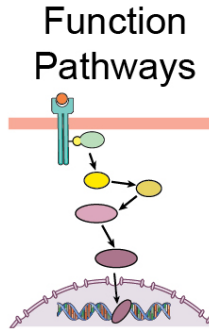
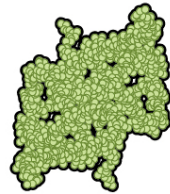
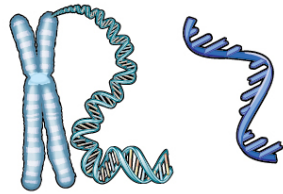
- 5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Pathobiology of PAH: New Ontology of PAH based on Endophenotypes

GENE → mRNA → PROTEINS → CELL → METABOLITES → VASCULAR → PATIENT

CARDIAC
Functions

Clinical events
History, Physical



Genome

Transcriptome

Proteome

Metabolome

Coagulome

Cell Biome

Imaging

Clinical Chemistry

Cardiopulmonary Physiology



NHLBI Lung Vascular Science Workshops 2010-2012

NHLBI Workshop



Strategic Plan for Lung Vascular Research

An NHLBI-ORDR Workshop Report

Serpil Erzurum¹, Sharon I. Rounds², Troy Stevens³, Micheala Aldred⁴, Jason Aliotta⁵, Stephen L. Archer⁶, Kewal Asosingh¹, Robert Balaban⁷, Natalie Bauer³, Jahar Bhattacharya⁸, Harm Bogaard⁹, Gaurav Choudhary², Gerald W. Dorn, II¹⁰, Raed Dweik¹, Karen Fagan³, Michael Fallon¹¹, Toren Finkel¹², Mark Geraci¹³, Mark T. Gladwin¹⁴, Paul M. Hassoun¹⁵, Marc Humbert¹⁶, Naftali Kaminski¹⁴, Steven M. Kawut¹⁷, Joseph Loscalzo¹⁸, Donald McDonald¹⁹, Ivan F. McMurtry³, John Newman²⁰, Mark Nicolls²¹, Marlene Rabinovitch²², Judy Shizuru²³, Masahiko Oka³, Peter Polgar²⁴, David Rodman²⁵, Paul Schumacker²⁶, Kurt Stenmark²⁷, Rubin Tuder¹³, Norbert Voelkel⁹, Eugene Sullivan²⁸, Richard Weinshilboum²⁹, Mervin C. Yoder³⁰, Yingming Zhao³¹, Dorothy Gail³², and Timothy M. Moore³²

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart
Association® 
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NHLBI Workshop: Improving Outcomes for Pulmonary Vascular Disease
Ivan M. Robbins, Timothy M. Moore, Carol J. Blaisdell and Steven H. Abman

American Thoracic Society Statement 2013

AMERICAN THORACIC SOCIETY DOCUMENTS



An Official American Thoracic Society Statement: Pulmonary Hypertension Phenotypes

Raed A. Dweik, Sharon Rounds, Serpil C. Erzurum, Stephen Archer, Karen Fagan, Paul M. Hassoun, Nicholas S. Hill, Marc Humbert, Steven M. Kawut, Michael Krowka, Evangelos Michelakis, Nicholas W. Morrell, Kurt Stenmark, Rubin M. Tuder, and John Newman; on behalf of the ATS Committee on Pulmonary Hypertension Phenotypes

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY (ATS) WAS APPROVED BY THE ATS BOARD OF DIRECTORS, SEPTEMBER 2013

RFA-HL-14-027 PVDOMICS 2014 (awarded 9/14) **Improve vascular disease molecular and clinical phenotype coupling**

- *Next generation of clinical studies*
- *Comprehensive of all WHO groups*
- *Utilize a consortia approach to characterize PH phenotypes*
- *Define endpoints and targets for clinical trials: new and meaningful surrogate and mechanistic biomarkers*



PVDOMICS Goals

- To perform comprehensive phenotyping and endophenotyping (genomic, proteomic, metabolomic, coagulomic, cell and/or tissue based) across the World Health Organization (WHO) classified PH clinical groups 1 through 5 as well as intermediate phenotypes (including those without overt PH) in order to deconstruct the traditional classification and define new meaningful subclassifications of patients with PVD.
- The long-term goal is utilization of endophenotypes/biomarkers for early diagnosis, at-risk screening, and personalized approaches for interventions and/or preventions of PVD.

Specific Aims are given in Protocol Section 2.1

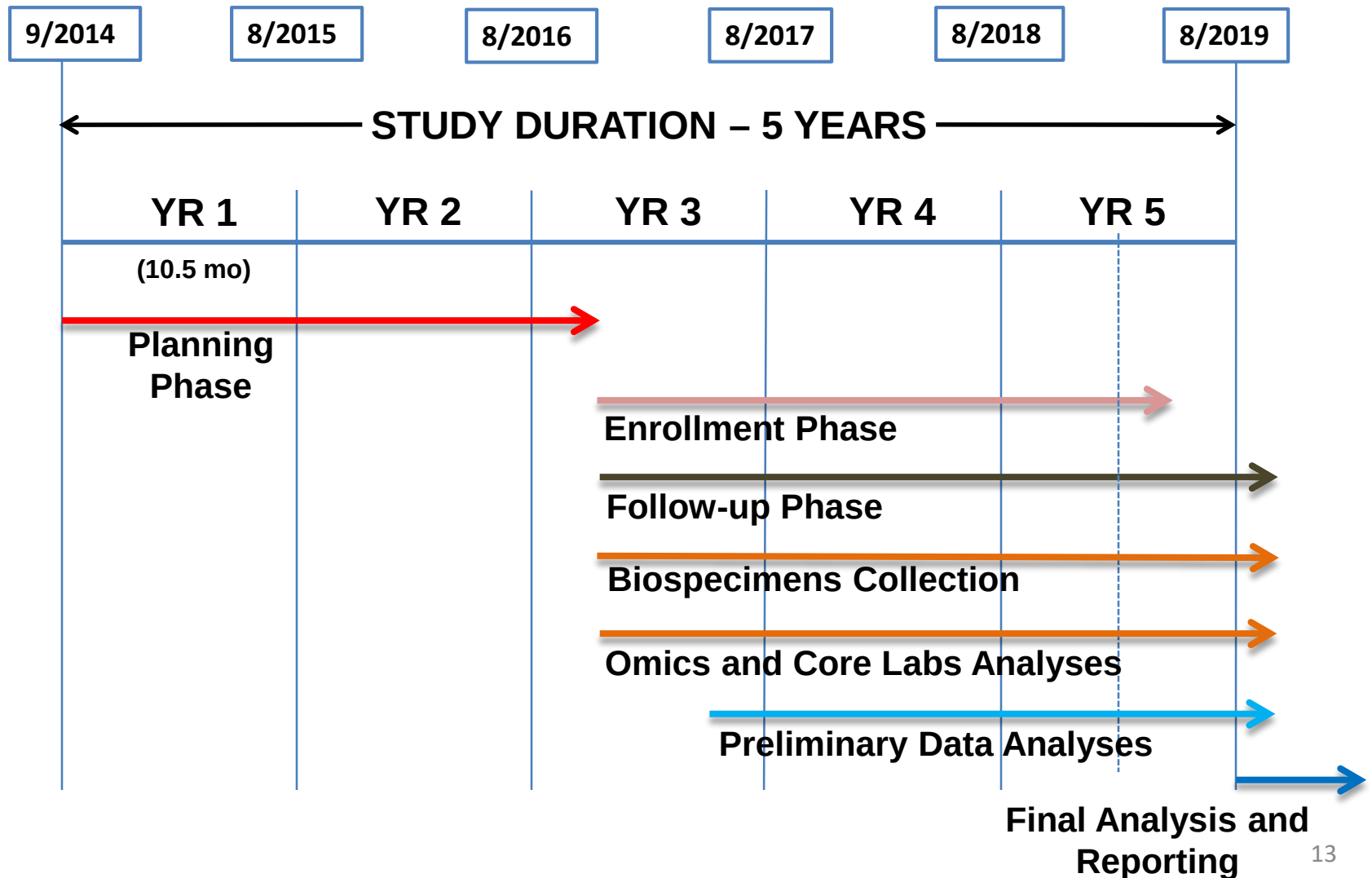
Protocol

- History
- Vitals
- HRQOL
- BIA
- Waist/hip measurement
- PFTs
- 6MWD
- Echo
- Cardiac MRI
- ECG
- Chest CT
- V/Q scan
- CPET (invasive or noninvasive)
- Sleep study
- Right heart catheterization
- Blood/urine
 - Clinical
 - OMIC
- Follow-up

Role of Study Coordinator

- Identify/recruit patients
- Consent patients
- Schedule visits and testing
- Perform assessments
- History forms
 - HRQOL forms
 - 6MWT
 - BIA
 - Hip/Waist measurements
 - Vital status
- Collect, process and ship
 - Blood
 - Urine
- Complete CRFs
 - Source documents
- Data entry
- Upload files/images to DCC
- Report AE/SAEs
- Maintain regulatory documents
- Attend and participate
 - Coordinator conference calls
 - Face-to-face meetings
- Prepare for site visits
- Communicate regularly with PI(s)

PVDOMICS Study Timeline



Participant Timeline

- Identify potential participants
- Consent
 - Adverse event reporting begins at time of consent
 - Needs to be signed ≤ 30 days before initial study visit/completion of F100
- Study visits (3-4) to be completed within 6 weeks of F100
 - Extension F410
 - Exceptions F411
 - Schedule of tests and measurements covered later
- 2 week follow-up call
- Yearly vital status call

Annual Contact by Telephone Up To 3.5 Years

- Vital status
- Occurrence/date of lung, heart or heart-lung transplantation
- Cause of death ascertained by the site investigators