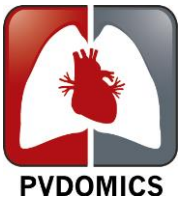
Pulmonary Vascular Disease Phenomics Program - L-PVDOMICS



Study Protocol
Version 1.2

February 21, 2020

1. Introduction

PVDOMICS aims to redefine the endophenotypes of pulmonary vascular disease coupling enhanced phenotyping and multidimensional OMICS across the spectrum of pulmonary vascular disease inclusive of World Symposium of Pulmonary Hypertension (WSPH) Group 1-5 patients, disease matched cohorts and controls. The strength of the PVDOMICS study design is its intense and extensive clinical phenotyping coupled with a large array of biological measures of multisystem function at one point in time. This unprecedented approach should yield abundant new information about the multiple causes of pulmonary vascular disease and their biological associations and further inform novel classification of disease. However, as the PVDOMICS network nears the 1,000 participant mark, it has become apparent to the investigators that the study design needs revision for realization of its full potential to validate and extend the new OMICS information. While our primary focus of PVDOMICS has been to better understand the biology and mechanisms of disease and to ultimately redefine clusters within and between traditional WSPH groups, the investigators believe there is a unique opportunity to utilize the OMICS for predictive analyses by including longitudinal data including serial OMICS and clinical outcomes. Furthermore, without serial testing, there is limited data on stability of OMICS data over time and/or the degree to which non-genomics measurements may be dynamic.

Investigators have had numerous discussions about how to best balance the feasibility of meeting target enrollment of participants with maximizing the output of this program. Given the completed enrollment of WSPH group 1 participants and the slower paced enrollment of WSPH Group 2 and 3 participants, a re-examination of our initial WSPH Group target numbers and participant accrual numbers was performed. This analysis concluded that for the WSPH Groups 1-3, a lower enrollment target is feasible and would not jeopardize or detract from the statistical design of the parent PVDOMICS study. Further, a reduction of target enrollment in Groups 2 and 3, would enable reallocation of resources to a longitudinal study that would enhance the PVDOMICS program. About 400 participants (PH, comparators and controls) will take part in this follow-up study at the clinical centers who participated in the parent PVDOMICS study.

Thus, an extension of observation and longitudinal follow-up and re-measurement of multiple variables is needed for the following reasons:

1) follow-up to determine participant function and survival related to the initial clinical phenotype and OMICS features. This seems essential because the initial study is limited to a short baseline period for measurement and ignores the natural disease history for participants already on therapy and response to therapy for incident participants at time of enrollment;

2) validation of the reproducibility and variance of OMICS measurements over time. This will be essential to validate the baseline data of the parent study;

3) clinical follow-up to determine the predictive value of the many physiological and OMICS measures made in the parent study. In addition, all enrollees will be queried for occurrence of events including:
    a) Hospitalization and any cardiovascular or pulmonary admission;
    b) Transplantation (lung, heart, liver, kidney or other, excluding corneal transplantation)
4) determine if shifts in OMICS features associate with drifts in clinical phenotype.

This approach of the longitudinal follow-up study (L-PVDOMICS) is expected to lead to improved understanding of disease mechanisms, natural history, response to treatment, disease progression and clinical outcomes. Further, it should enable us to correlate new and dynamic OMICS signatures identified in study enrollees with longitudinal clinical outcomes. Ultimately, this pilot study should lead to in depth projects testing novel personalized and precision medicine approaches for the treatment of pulmonary hypertension by linking newly defined endophenotypes from the original study enrollees to longitudinal testing and outcomes. The PVDOMICS network sites have uniformly expressed a desire to extend the enrollment period beyond the original termination date to collect longitudinal data on enrolled subjects to address the questions posed above.

2. Objectives

2.1 Specific Aims:

1. To retest participants at a minimum 6 month interval from initial evaluation using a core set of clinical and OMICS features. This will include survival, clinical staging, clinical group assignment, 6-minute walk, echocardiography, and blood for a broad collection of selected OMICS tests, to include proteomics and other variables found to be informative in the initial set.

2. Associate and compare OMICS data with clinical sets and OMICS clusters between baseline and follow-up interval, with attention to reproducibility, predictive capacity as biomarkers for diagnosis, disease progression, phenotypic changes, functional capacity, therapeutic response and survival.

2.2 Hypothesis

We hypothesize that serial deep OMICS phenotyping of PH with longitudinal follow-up will uncover new understanding of disease mechanisms, the stability of OMICS patterns over time, disease progression, response to therapeutics, and outcome data invaluable to the field.

2.3 Study Design

2.3.1 Organizational Structure of the Study

Please refer to parent study protocol.

3. Study Participants

Only participants who completed the parent PVDOMICS study will be approached for the L-PVDOMICS Study. This includes all participants: PH, comparators and controls with a minimum 6 months post-enrollment in PVDOMICS.

See the parent PVDOMICS protocol for full details of inclusion/exclusion criteria.

3.1 Inclusion criteria

- Any PH, comparators or control participant previously enrolled in the parent PVDOMICS protocol with a minimum of six months post-enrollment
- Dialysis dependent renal function since the parent study acceptable

3.2 Exclusion criteria

Definition of Level of participant is given in Section 4.1.

Participant Level 1:

- Previously received a heart and/or lung transplant
- In the clinician's opinion, too ill to perform L-PVDOMICS testing even if limited testing. \
- Participants who withdrew from the parent PVDOMICS study
- Pregnant or nursing
- Concurrent participation in any pulmonary hypertensioninvestigational drug study or other blinded placebo-controlled drug clinical trial

Participant Level 2:

- Previously received a heart and/or lung transplant
- Participants who withdrew from the parent PVDOMICS study

Participant Level 3:

- Participants who withdrew from the parent PVDOMICS study

4. Data Collection

4.1. Study Visit

We will capture longitudinal OMICS on as many participants from the parent cohort as possible. The study includes all participants who were eligible (i.e., > 6 months post enrollment). Due to the varied time to follow-up and the potential logistic barriers, e.g., distance from center, comparator incentive, the plan will be to obtain the data in a multi-tiered approach to capture as much longitudinal data as possible (see below for Levels 1-3 participation). This will include a minimal follow-up data set/chart review for participants who could not participate or were willing to agree to a full follow-up (Levels 2, 3), and a more comprehensive follow-up for those

able to return to primary site to perform follow-up standard of care testing plus an echocardiogram (Level 1 participation). For parent PVDOMICS participants who died or underwent transplantation, outcomes and important clinical studies performed at least 6 months following initial enrollment, but prior to the definitive outcome will be recorded. To achieve this goal, the protocol is practical, relatively inexpensive and minimizes participant burden. This will increase opportunities to learn from all PVD enrollees, not just a single type of PH.

There will be three levels of participation which will be described in further detail. Participants will consent to one level depending on their medical history and willingness to participate.

Level 1 Participation *(preferred)*
The participants, (PH, non-PH comparators, and controls who consent to Level 1 participation) will undergo biospecimens collection (blood and urine), which will be processed and stored at the Biorepository Core at the Data Coordinating Center at the Cleveland Clinic. Where feasible and not contraindicated, all participants who consent to Level 1participation will undergo a uniform set of assessments usually at a single visit that will include the following.

Level 1 will occur during a follow-up visit to the clinical site and complemented with electronic health record data extraction. [A corneal transplant does not exclude participant from participating in Level 1). Data collection and testing will include:

1. History & limited physical exam, limited demographics
2. Medications, prescription and over-the-counter
3. Quality of Life questionnaires (SF-36, Minnesota Living with Heart Failure (MLHF) and EmPHasis-10)
4. Clinical worsening and adverse events (described in section 4.2.3)
5. WHO Functional Class as measure of disease severity
6. Six Minute Walk Test (6MWT)
7. BMI/Anthropomorphics
8. Echocardiogram (clinical standard-of-care/or research study for disease subjects, and disease comparators)
9. Clinical blood draw – CBC with diff, metabolic panel
10. Urine collection
11. Fasting blood draws for OMICS (metabolomics, proteomics, RNA/miRNA, and also DNA for methylation follow-up. Other labs (e.g., NT-pro BNP, lipid panel, inflammation panel, iron metabolism panel, uric acid, insulin, HOMA-IR)
12. If patient had testing (including RHC, echocardiogram, cardiac MRI, CPET, PFT, sleep study, chest CT scan, ECG) within 3 months (either side) of follow-up visit, include clinically available data.

Level 2 Participation

If participant is alive, but does not consent to a Level 1 in-person visit, they can participate at Level 2 if they are willing to consent to a phone call that includes Level 1 Participation parameters 1-5:

1. Medical history since last visit, limited demographics;
2. Medications review, prescription and over-the-counter;
3. Completion at home of Quality of Life questionnaires (SF-36, Minnesota Living with Heart Failure (MLHF) and EmPHasis-10):
4. Clinical worsening and adverse events review (cardiovascular and lung related hospitalizations)
5. WHO Functional Class as measure of disease severity
6. If patient had testing (including RHC, echocardiogram, cardiac MRI, CPET, PFT, sleep study, chest CT scan, ECG) within 3 months (either side) of L-PVDOMICS enrollment date, include clinically available data.

Level 3 Participation

Any person not agreeing to participate at Level 1 or 2 can participate at Level 3. For this level, a medical record review will collect clinically available data (including RHC, echocardiogram, cardiac MRI, CPET, PFT, sleep study, chest CT scan, ECG) within 3 months (either side) of L-PVDOMICS enrollment date. If the participant had a heart and/or lung transplant or died since the parent study, the date of transplant or death will be documented per the parent PVDOMICS protocol and the medical record review will collect data within 3 months prior to the transplant or death date except when the transplant or death occurred before 6 months after the parent study enrollment. In this case, all clinically available data should be collected from after the parent study up to the transplant or death.

4.2 Evaluations and Data Collection

4.2.1 Demographics and Updated Family History

As birth date, gender, race, and ethnicity were asked in the parent PVDOMICS study, only the zip code of most recent domicile and race, if not provided previously, will be recorded for L-PVDOMICS.

4.2.2 Quality of Life Questionnaires

Quality of life questionnaires will be completed by each participant consenting to Levels 1 or 2. This includes the 36-item health survey SF-36v2®, the Minnesota Living with Heart Failure (MLHF) Questionnaire and the EmPHasis10 survey. In addition, WHO Functional Class will be recorded.

4.2.3 Comorbid Conditions since Completion of Parent PVDOMICS Study

Tobacco use (current, total pack years)
Alcohol use (Current, number of drinks per week),
Diabetes Type I, Type II, therapy (diet, oral agent, insulin)
Sleep disordered breathing (current type of treatment)
Hypertension (medications)
Cardiac diagnoses (arrhythmias, valve disease, rheumatic disease, CAD, etc.)
Pulmonary diagnoses
Renal insufficiency (medications)
Liver disease
Obesity
Recent diet or methamphetamine drug exposure (name of medication and year(s) of exposure)
Malignancy aside from localized non-melanoma skin cancer
Exposure to chemotherapeutic drugs (e.g., cyclophosphamide, multi-tyrosine kinase inhibitors)
High altitude exposure (duration)
Estrogen containing medication exposure (duration)
DVT or PE or hypercoagulability
Relevant surgical history since completion of parent PVDOMICS study:

- Cardiac surgery (type)
- Atrial septostomy
- Pulmonary surgery (type)
- Gastric bypass or banding
- Pacemaker
- Defibrillator

4.2.4 Medications

A complete list of medications including prescription and over the counter or homeopathic products will be compiled that provides a snap-shot of the participant's current drug regimen. Duration will be identified for intravenous or subcutaneous prostanoids and chemotherapeutic medications. Oxygen use should be described, including description of dose and when used (night, day, exertion). Changes in PH therapy since enrollment should be noted.

4.2.5 Clinical Worsening and Adverse Event Assessment since Completion of Parent PVDOMICS Study

All enrollees will be queried for occurrence of events including:

A. Hospitalization (any or cardiovascular/PH admission),
B. Transplantation (lung, heart),
C. Need for new PAH therapy (oral or parenteral prostanoid), increase in WHO Functional Class),
D. Referral to hospice for cardiac/pulmonary hypertension reasons,

E. Placement of atrial septostomy since parent PVDOMICS study.

4.2.6 Physical Measurements

Vital Signs
Height, weight, heart rate, seated blood pressure, oxygen saturation (room air, or specify oxygen amount), temperature and respiration rate. .

Waist – Hip Ratio
The waist circumference will be measured as illustrated in the PVDOMICS Manual of Operations.

4.2.7 Six Minute Walk Test (6MWT)

6MWT will be performed in accordance with American Thoracic Society guidelines. Resting O2 sat and heart rate will be obtained as described in the PVDOMICS Manual of Operations. A pre- and post-walk Borg Dyspnea score will be recorded.

4.2.8 Echocardiography

All participants in the L-PVDOMICS Level 1 testing will undergo a standardized PVDOMICS research transthoracic Echo exam as outlined in the PVDOMICS Manual of Operations. Individuals who will be exempted include:

- Clinical or hemodynamic instability requiring immediate therapy
- Inability to communicate with the sonographer/follow commands for any reason and/or provide consent (psychosis, agitation, etc.)

The PVDOMICS Echo protocol should be followed as outlined in the PVDOMICS MOP, the only change from the baseline study echo is that a bubble study is no longer required. (The bubble study should have been performed at baseline visit when needed.) The optional 3D imaging protocol remains elective. A clean baseline ECG is required and each clip should include three complete cardiac cycles.

The Echo for the L-PVDOMICS study will be performed only by sonographers previously or newly qualified and trained as outlined in the PVDOMICS Echo chapter of the PVDOMICS Manual of Operations.

For those subjects which cannot have a research echo and must have a clinical exam for other reasons it is important that the site coordinator give the sonographer instructions and a copy of the PVDOMICS echo protocol prior to starting the exam. This is to avoid PHI on the echo images as well as lack of data collection. A three-beat loop should be collected and the additional RV heart views and Doppler recorded per protocol.

The clinical sites' echo reports and images of the study subjects will be readily available for clinical decision-making by the local clinical teams and study investigators.

All of the Echo studies will be collected as DICOM files and saved to a disk directly from the echo system and uploaded by the local study coordinators into the AG Mednet portal and sent to the Echo Core Lab server for analysis. Each study should be uploaded separately and as soon as possible for analysis. The Echo variables for the L-PVDOMICS dataset inclusion will be derived solely from the Core Lab data.

Justification

The PVDOMICS Transthoracic Echocardiography will objectively reveal:

- Anatomy and morphology of the cardiac chambers
- Presence or absence of structural heart disease
- Hemodynamic status, volume status and functional performance (systolic and diastolic) of the RV and the LV
- Clinical features predominantly consistent with the WHO Group 2 PH.
- Gross anatomy and morphology of great vessels (aorta; main pulmonary artery)
- Presence or absence of a pericardial effusion

4.2.8 Sleep Study

Investigators are encouraged to obtain a Nox3 sleep study to be performed within 6 weeks of enrollment in the L-Omics project (Level 1). If the Nox3 sleep study cannot be obtained, then overnight oximetry is encouraged in the patient's usual sleep setting (i.e., room air, CPAP, BIPAP, O2).

4.3 Biospecimen Collection

Blood (cells, serum, plasma) and urine samples will be collected from Level 1 participants for molecular OMICS analysis and also clinical labs including:

- Clinical Labs:
  - CBC with differential
  - Comprehensive metabolic panel
  - NT-pro BNP
  - Lipid panel
  - Inflammation markers
  - Iron metabolism
  - Uric acid
  - Insulin (with calculation of HOMA-IR)

- OMICS Labs:

- Metabolomics
- Proteomics
- RNA/miRNA
- DNA for methylation

Details of amounts and types of specimens are given in the PVDOMICS Manual of Operations.

4.4 Additional Data Collection

If patient had testing (RHC, echocardiogram, cardiac MRI, CPET, PFT, sleep study, CT scan, V/Q scan) within 3 months (either side) of follow-up visit, clinically available data will be collected.

If a chest CT scan was completed, the CT images and final radiologist's report will be uploaded via Data Coordinating Center's secure portal for review the Lung Imaging Core.

4.5 Longitudinal Follow-up

Longitudinal follow-up will occur as per the parent PVDOMICS protocol. All participants, or their designated contacts, will be contacted by telephone and/or letter at least annually after enrollment up to the end of the study. Vital status and occurrence/date of any lung, heart or heart-lung transplantation will be determined from this contact or by using center medical records. Cause of death will be ascertained by the site investigators.

5. Other Considerations

Clinical worsening outcomes that may be analyzed include, but are not limited to, the following:

- Hospitalization
- Death
- Transplantation (heart, lung, other)
- Need for new PAH therapy (oral/parenteral prostacyclin)
- Increase in WHO Functional Class
- 15% decrease in 6 minute walk distance
- Referral to hospice
- Need for atrial septostomy or other palliative procedure for PAH

6. Regulatory Considerations

These are unchanged from the parent PVDOMICS protocol for IRB, confidentiality, participant consent and the Observational Safety and Monitoring Board. However, for the longitudinal

study, adverse events will be collected only for Level 1 participant events that occur during the Six Minute Walk test.

7. Ancillary Studies

See parent PVDOMICS study.